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Renal Osteitis Fibrosa Cystica. Roport of a Case with Discussion of Metabolic Aspects. FULLER ALBRIGHT, M.D., TRUMAN G. DRAKE, M.D., AND HIRSH W. SULKOWITCH, M.D. 377

An Attempt to Condition Adrenalin Hyperglycemia. W. HORSLEY GANTT, S. KATZENELBOGEN AND R. B. LOUCKS. 400

The Occurrence of Constitutional Reactions in the Treatment of Hay Fever and Asthma: Analysis of the Causative Factors. FRANK F. FURSTENBERG, M.D. AND LESLIE N. GAY, M.D. 412

On the Prolonged Coagulation Time Subsequent to Anaphylatic Shock. HARRY EAGLE, C. G. JOHNSTON, AND I. S. RAVDIN 428

Book Reviews 439
Index 445

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RENAL OSTEITIS FIBROSA CYSTICA

Report of a Case with Discussion of Metabolic Aspects[1]

FULLER ALBRIGHT, M.D., TRUMAN G. DRAKE, M.D., AND HIRSH W. SULKOWITCH, M.D.

From the Medical Department of the Massachusetts General Hospital

Submitted for publication August 8, 1936

This paper has three objects: (1) to call attention to a disease entity with certain bizarre manifestations; (2) to report in detail observations made upon a patient suffering from this disease; (3) to discuss on the basis of data obtained from this patient the relation of each feature of the syndrome to the others.

The authors are aware of two other cases which belong to the disease entity under discussion—one reported by Wentworth and Hubbard (1), and one seen in consultation by one of us (F. A.) but unfortunately never completely reported.[2] The condition is characterized by certain striking lesions which, when encountered for the first time, are apt to be considered as non-related phenomena occurring in one individual. But when one encounters these same features in three different individuals it is probable that they are related phenomena and the next question deals with the relation of one feature to the others.

The salient aspects of the syndrome are marked renal insufficiency which has lasted a long time, phosphate retention with a high serum inorganic phosphorus level, slight reduction in the serum calcium level, marked acidosis, calcium deposits in the neighborhood of joints, extreme calcification of the media of arteries (the Mönckeberg type of arteriosclerosis), osteitis fibrosa generalisata of all bones, and enormous enlargement of all parathyroid tissue. The condition is probably the adult counterpart of so-called renal rickets.

[1] This paper was read in abstract before the Association of American Physicians at Atlantic City, May, 1936. (V. *Transactions of the Association of American Physicians*, 1936.)

[2] This case was reported in abstract as Case no. 23A by Castleman and Mallory (22).

Case History. F. L. S. (M.G.H. No. 349407).[3] A 45-year-old male American clerk was admitted to the Massachusetts General Hospital from the Out Patient Department November 5, 1935, complaining of intermittent generalized itching for a period of about two years, and painful swellings on the fingers of the right hand of two months' duration.

The onset of the present condition apparently dated back some 23 years at which time he had an illness associated with painless swelling of the ankles, followed by generalized "dropsy". At this time he was admitted to a hospital in Philadelphia where he was kept for five months, after which he was discharged with a diagnosis of "incurable Bright's Disease". After discharge two physicians were called in, one of whom said that the disease was fatal, while the other prescribed a salt-free diet containing no red meat, and Epsom salts to be taken daily. After 5 months on this diet the patient was free of edema and was able to sit up in a chair. A year after discharge he felt well enough to return to work as a clerk. For the next 20 years he was apparently well except for a little nervousness which he had always had, and nycturia of one time. Throughout this period the patient adhered to the low salt diet containing no red meat.

Two and a half years before admission he began to feel "run-down" and increasingly nervous, and developed generalized itching, which at night was often intense. He consulted an osteopath who examined his urine and told him he had mild diabetes and kidney disease. The patient was placed on a low-sugar, low-salt diet and was informed that red meat would not be harmful to him. He was given intramuscular injections of Lederle's liver extract and in addition was placed on a proprietary preparation "Bovinine". On this therapy the itching became less severe and the patient was subjectively improved. Eleven months before admission the pruritus, nervousness, and fatiguability again became more severe, and the nycturia increased to 3 or 4 times. Again he consulted the osteopath who gave him weekly injections of Lilly's liver extract until three weeks before admission.

Two months before admission the patient developed firm tender swellings on the 2nd, 3rd, and 4th fingers of the right hand accompanied by a burning type of pain. Hot fomentations relieved the pain but the nodules persisted. Shortly thereafter he developed a tender swelling upon the right elbow which persisted for about a week. He then had in succession similar but less persistent swellings in the region of the right shoulder, left shoulder, left elbow, and ulnar aspect of the left wrist. There was no involvement of the joints themselves, but in each case movement of the adjacent joints increased the pain in the nodules.

Of interest in the past history is the fact that he had had scarlet fever at the age of 10 but with this exception his memory gave no data.

Physical examination showed a fairly well developed but thin middle-aged man in no acute distress. He was ambulatory and cheerful. His complexion

[3] This was reported as one of the Case Records of the Massachusetts General Hospital, *New England J. Med.*, **214**: 320, 1936.

was light and the skin was dry, pale, and of a sallow hue. The mucous membranes were moderately pale and the breath was uriniferous. The fundi showed narrowed arteries giving the silver-wire appearance, and in the left eye there was evidence of an old hemorrhage. The teeth were in poor repair. Over the precordium there was a systolic and an early diastolic murmur suggestive of slight aortic regurgitation. The heart was not enlarged. The blood pressure was 165/90; the peripheral arteries were markedly thickened and somewhat tortuous. The liver edge was just palpable on deep inspiration. The prostate felt moderately enlarged but otherwise normal. There were several cystic swellings about the first interphalangeal joint of the right index finger; a similar nodule was found at the right elbow.

The urine showed a large amount of albumin, and a green reaction without precipitate to Benedict's solution. The sediment showed an occasional white blood cell with rare red cells and granular casts. The specific gravity was 1.008 on admission and remained fixed between 1.010 and 1.012 during a concentration test. The red blood cell count was 3,800,000 and the hemoglobin 65%(T). Some doubt must be thrown on these values because his oxygen capacity was later found to be only 7.69 vols. per cent. Leucocytes 12,000, 63% polymorphonuclears. The red cells and platelets appeared normal. A Hinton test for syphilis was negative. The non-protein nitrogen of the whole blood was elevated to 120 mgms. %, with a uric acid value of only 4.4 mgms. %, which was normal for the method used; the carbon dioxide combining power of the plasma was decreased to 37.8 vols. %. The fasting blood sugar was 112 mgms. %. An intravenous phenolsulphonephthalein test showed less than 5% of the dye excreted in each of three specimens, collected at 15 minutes, 30 minutes, and 60 minutes. The fasting serum inorganic phosphorus level, 9.8 mgms. %, was markedly elevated (*cf.* high blood non-protein nitrogen) and the serum calcium level was slightly depressed, 8.2 mgms. %. The phosphatase level in the serum was elevated 9.4 Bodansky units.

Before the remaining findings are given it may be of interest to see what was thought concerning the patient at this stage of the investigations. The essential facts recorded a patient whose only complaint was itching, but who did have nycturia, who showed on physical examination, besides a high blood pressure and retinal changes, some deposits around the joints, and whose laboratory studies showed evidence of marked renal insufficiency. The *admission diagnosis* was chronic glomerular nephritis, probably complicated by gout, in a person with rheumatic heart disease. The one extraordinary thing about the case was the 23-year history of renal disease with the long period of freedom from symptoms.

The first surprise and the diagnosis came when the right hand was x-rayed and the lesion was found to be due not to gout but to calcium deposits around the

FIG. 1. CALCIUM DEPOSITS ABOUT THE FINGER JOINTS

joints (see figs. 1 and 2). This evidence, together with that already stated, was sufficient to bring about at once the recognition by one of us (H. W. S.) of the case as belonging to the disease entity under discussion.

Accordingly, this patient was x-rayed to see whether the predicted bone changes and arterial changes were present. They were. The bones of the pelvis showed decalcification. The skull had the thin "moth-eaten" appearance which is seen in hyperparathyroidism with bone disease (see fig. 3). The jaws showed absence of the lamina dura about most of the tooth sockets, and the bone was radiolucent and had a ground glass appearance. The teeth, contrasted with the bone, were of normal density. The heart contours were at the upper limit of normal and there was questionable enlargement of the left ventricle. There was marked arteriosclerosis of the arch and descending aorta. In all of the films the large and small arteries showed an extreme degree of sclerosis (see fig. 4); in

FIG. 2. CALCIUM DEPOSITS ABOUT THE ELBOW JOINT

some of the vessels this was due to Mönckeberg type of medial calcification. There were masses of homogeneous calcification without trabeculation surrounding the proximal interphalangeal joints of the right second, third, and fourth fingers. Similar calcified areas were scattered along the phalanges of these fingers. Both elbows and acromioclavicular joints showed similar calcified masses. They were present also in the soft tissue proximal to the pedal phalanges. An intravenous pyelogram showed the kidneys to be extremely small, and they secreted very little of the dye.

The patient continued to feel well and was remarkably active considering the degree of renal insufficiency. He was able to coöperate for metabolic studies, which will be discussed below. After two weeks in the hospital he developed a

severe diarrhea which was relieved by paregoric, and nosebleeds which stopped spontaneously. About four weeks after entry a tibial biopsy was made under local anesthesia. Four days after this the patient was suddenly seized with severe pain between the shoulder blades which spread to the left chest and left upper abdomen with some radiation down the left arm. Accompanying these symptoms were dyspnea, ashen pallor, sweating, a rapid thready pulse, poor heart

FIG. 3. SKULL, SHOWING THIN "MOTH-EATEN" APPEARANCE OF BONE

sounds, and a drop in blood pressure to 60/50. An electrocardiogram taken shortly thereafter showed a left bundle branch block, increase of the P-R interval to 0.22 sec., absence of Q_4, slight irregularity of the rhythm, and a rate of 60 per min. An electrocardiogram taken before the episode had been essentially normal. The patient failed rapidly and lapsed into coma, dying 5 hours after the onset of what appeared to be coronary thrombosis, 30 days after admission to the hospital.

Autopsy performed two hours after death verified the clinical impressions in

practically every detail. The extremely atrophic pair of kidneys weighed only 85 gms. and were granular, the cortex measuring only 2 mm. in thickness. The pelves were entirely negative and Dr. Tracy B. Mallory felt quite sure that pyelonephritis could be ruled out. Microscopic sections of the kidneys showed very few glomeruli and no evidence of active glomerulitis. The findings were thought

FIG. 4. X-RAY PICTURE OF THIGHS TO SHOW EXTENSIVE CALCIFICATION OF ARTERIES

to be consistent with a very stationary if not healed form of chronic glomerular nephritis. All four of the parathyroid glands were tremendously enlarged and pale; the largest weighed nearly 5 grams (normal about 60 mgms.); the total weight of parathyroid tissue was 11 grams (fig. 5). Microscopically, the parathyroid glands showed diffuse hyperplasia, all of the cells being of the chief cell variety. The cells were not slightly enlarged as seen in parathyroid adenomas,

nor markedly enlarged with highly vacuolated cytoplasm as in primary hyperplasia (see fig. 6 and discussion below). The vessels throughout the body showed extensive medial calcification. The coronary arteries showed in addition atheromatous deposits with marked narrowing of the lumina. There was a fresh clot in one of them and also a clot loosely adherent to the wall of the right auricle. Microscopically, these both proved to be ante-mortem clots. The heart showed typical rheumatic valvular disease involving both mitral and aortic valves. The bones everywhere were soft. In the end plates of several of the vertebrae there were herniations of the adjacent nuclei pulposi (*Schmorlsche Knötchen*) (see fig. 7).

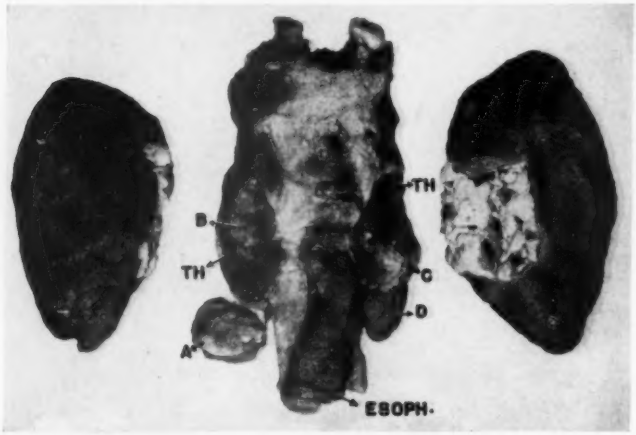

FIG. 5. DISSECTION OF NECK ORGANS SHOWING ENLARGED PARATHYROIDS *A*, *B*, *C* AND *D*

(A) THE BONE DISEASE IS OSTEITIS FIBROSA AND NOT OSTEOMALACIA

In figures 8 and 9, it will be seen that the histological bone abnormalities in this man were exactly like those seen in a patient with osteitis fibrosa generalisata due to hyperparathyroidism. Bone biopsies from both patients showed evidence of rapid bone destruction (osteoclasts +++), evidence of rapid bone repair (osteoblasts +++), evidence that bone matrix which was being laid down was being calcified (normal width of osteoid seams), and fibrosis of marrow spaces. Shelling and Remsen (2) found similar bone changes in their case of undoubted renal rickets.

From a pathological point of view the bone condition would have to

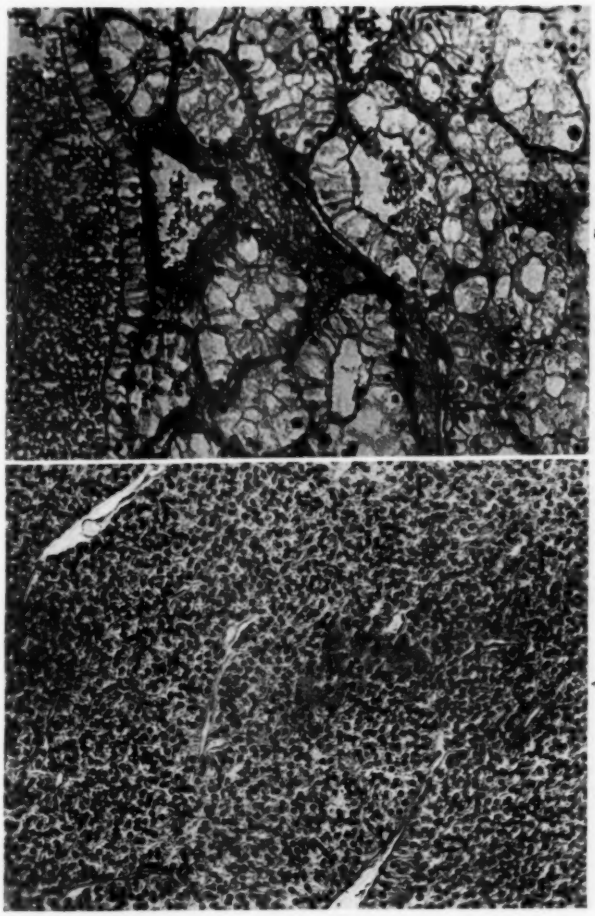

FIG. 6. MICROPHOTOGRAPHS TO ILLUSTRATE DIFFERENCE IN PARATHYROID HISTOLOGY BEWEEN HYPERPLASIA SECONDARY TO RENAL INSUFFICIENCY, AS OBSERVED IN THE PRESENT CASE (*A*) AND SO-CALLED PRIMARY HYPERPLASIA (*B*)

be classified, therefore, as osteitis fibrosa generalisata. It is not osteomalacia because that condition is characterized by a failure of calcium to be deposited in the newly laid down bone matrix (wide osteoid seams), by very few osteoclasts, and by much less evidence of fibrosis. The only histological bone change which the two conditions have in common is an increased number of osteoblasts. The bone

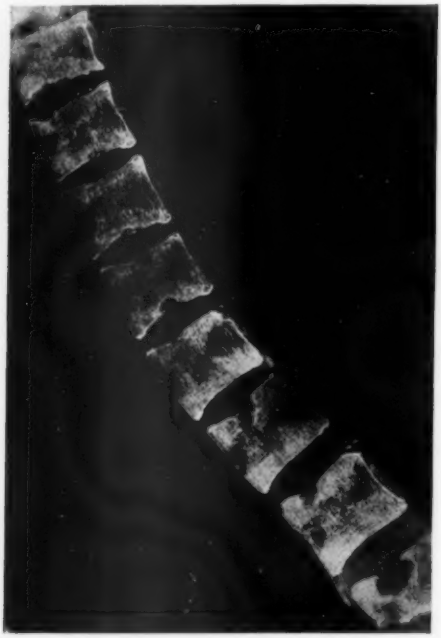

FIG. 7. X-RAY PICTURE OF LONGITUDINAL SECTION OF VERTEBRAE OBTAINED AT AUTOPSY

Note herniations of nuclei pulposi

changes in true rickets, of course, are the same as those in osteomalacia with some additional changes at the growing epiphyses.

From the above it is clear that renal rickets, at least as judged by the case cited, is not rickets at all. This terminology came into being in all likelihood because the x-ray appearance of the epiphyseal lines in

renal rickets is very similar to that in true rickets. Since the condition under discussion is probably the counterpart in the adult of renal rickets, if one were to adopt a consistent though wrong nomenclature, one would have to call this condition renal osteomalacia. Renal osteitis fibrosa generalisata has been chosen in the interests of accuracy rather than consistency. The term renal rickets has gained such wide usage that it seems unwise to attempt to change it now.

FIG. 8. MICROPHOTOGRAPH OF BONE BIOPSY TAKEN DURING LIFE OF PATIENT REPORTED IN THIS PAPER

If one were convinced that the bone changes were the result of the excessive production of parathyroid hormone, one could call the whole syndrome renal hyperparathyroidism, with the tacit assumption that hyperparathyroidism implied an accompanying osteitis fibrosa generalisata. Some evidence against this point of view will be discussed below. In this connection it should be pointed out that hyperpara-

thyroidism, when it produces osteitis fibrosa generalisata in children, does not produce x-ray changes at the epiphyses (3) (4) (8). This would be an additional argument that the bone changes in renal rickets are not due to the secondary hyperparathyroidism.

FIG. 9. MICROPHOTOGRAPH OF BONE BIOPSY OF A PATIENT SUFFERING FROM OSTEITIS FIBROSA GENERALISATA DUE TO HYPERPARATHYROIDISM

(B) CAUSE OF PARATHYROID ENLARGEMENT

It is now well established that a hyperplasia of the parathyroid glands may occur in the presence of marked renal insufficiency (5)

(6) (7). Excessive enlargement, as seen in our patient and in other cases of renal osteitis fibrosa and renal rickets, is presumably the result of marked renal insufficiency lasting a long time. The fact that marked renal insufficiency does not usually last a long time probably explains why the condition is so rare.

The hypothesis was advanced by Albright, Baird, Cope, and Bloomberg (8) that the cause of the hyperplasia was the phosphate retention. They argued that, since one of the actions of the parathyroid hormone is to bring about an increased excretion of phosphate in the urine and to lower the inorganic phosphorus level in the blood, it seemed possible that any state of affairs, such as renal insufficiency, which hindered this function might be attended by a compensatory hypertrophy of the parathyroid glands. In some recently published experiments in our laboratory parathyroid hyperplasia has been produced in rabbits by phosphate injections.[4]

(c) CAUSE OF OSTEITIS FIBROSA GENERALISATA

For those who believe that the parathyroid hormone acts directly on bone tissue (9) (10) the finding of osteitis fibrosa in such a case of secondary hyperparathyroidism must be very reassuring; for the other school of thought the finding is disquieting. It is the belief of one of us (F. A.) that the hormone does not act on bone tissue. This will be the subject of another communication. Some of the outstanding reasons for this alternative belief are: (a) the fact that bones are not abnormal in hypoparathyroidism; (b) the fact that patients with primary hyperparathyroidism often exhibit no evidence of bone disease; (c) the fact that bone disease in patients with primary hyperparathyroidism can be made to regress by the use of diet alone although the degree of hyperparathyroidism remains the same. The question, therefore, arises whether there is any other way of explaining the bone disease in the syndrome under discussion.

The first possibility is that the bone absorption may have been due to the acidosis resulting from the renal insufficiency. Dr. John Talbott was kind enough to determine the acid-base balance of arterial

[4] Drake, T. G., Albright, F., and Castleman, B.: Parathyroid Hyperplasia in Rabbits Produced by Parenteral Phosphate Administration. *J. Clin. Invest.*, **26**: 203, 1937.

serum of this patient at a time when he was ambulatory and complaining only of his itching. The electrolyte concentrations, expressed in m. eq. per liter of serum, were as follows:

Sodium	127.2	Chloride	106.1
Calcium	4.5	Carbonate	11.6
Potassium and magnesium*	7.0	Proteinate	14.8
Total fixed base	138.7	Phosphate	3.7
		Total determined acids	136.2

* This concentration is calculated by difference.

pH of arterial serum	7.22
Alveolar pCO_2	30.5 mm. Hg.
Oxygen capacity	7.69 vol. per cent
Cell volume	20.2

Dr. Talbott gave the following interpretation: "The principle changes in the acid-base balance of the blood of this patient are in the concentrations of sodium and bicarbonate. Calcium, phosphate and proteinate concentrations are modified also. A normal concentration of chloride with a diminished concentration of sodium is very interesting. This electrolyte pattern is not unusual in patients with acidosis secondary to chronic nephritis. It is associated frequently with severe tubular damage. This acidosis is a type of metabolic acidosis related principally to the loss of fixed base rather than to an increased concentration of undetermined acids." Therefore, since chronic acidosis in itself will produce osteitis fibrosa (Jaffe, Bodansky, and Chandler (11)) it is of interest that this patient probably had had a marked acidosis for a long period of time.

Another mechanism has been advanced by Mitchell (12) to explain the bone changes in renal rickets. It is argued that since phosphates cannot be excreted in normal amounts by the kidneys they are excreted in excess into the gastro-intestinal tract taking calcium with them or there interfering with the absorption of calcium. Our patient fortunately had so few symptoms that he was able to cooperate in some metabolic studies (see Table I and Chart I).

From Table I it will be noted that this patient had more calcium and phosphorus in the feces and less, if anything, in the urine than the normals. His negative balances were likewise slightly greater than those of normals. The changes were not as large as one might expect

TABLE I

Metabolic data during four three-day periods on a neutral ash low calcium diet with data for comparison from normal controls and from a patient with primary hyperparathyroidism

THREE-DAY PERIOD	URINE VOLUME	CALCIUM				PHOSPHORUS			
		Urine	Feces	Intake	Balance	Urine	Feces	Intake	Balance
	cc.	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*
I	5030	0.12	0.42	0.27	−0.27	1.10	0.69	1.53	−0.26
II	5420	0.13	0.40	0.29	−0.24	1.12	0.67	1.68	−0.11
III	5870	0.10	0.45	0.30	−0.25	1.06	0.72	1.77	−0.01
IV	4100	0.09	0.38	0.21	−0.26	0.82	0.72	1.14	−0.40
Average.....	5105	0.11	0.41	0.27	−0.25	1.02	0.70	1.53	−0.20
Normal* controls...		0.13	0.32	0.33	−0.12	1.21	0.60	2.07	+0.26
Patient with hyperparathyroidism†.		1.31	0.19	0.31	−1.29	2.22	0.24	2.10	−0.36

* Average values calculated from Farquarson, Salter, Tibbetts and Aub (13) of 14 three-day periods on four normal individuals on a neutral low calcium diet.

† Bauer, Albright and Aub (14).

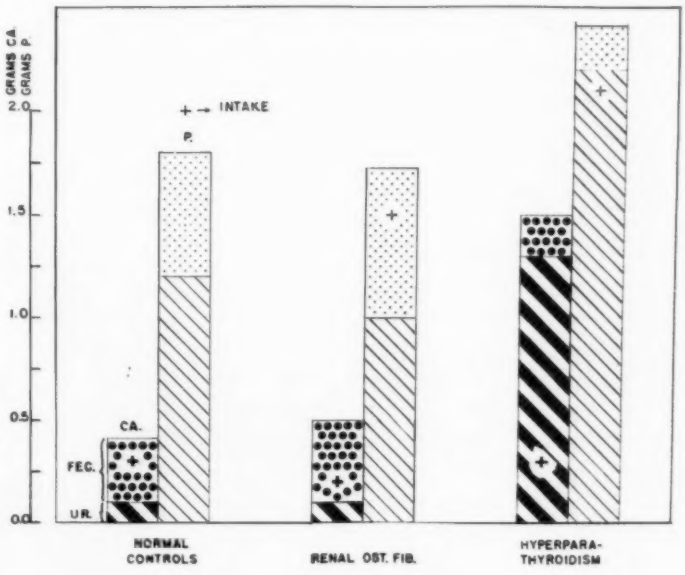

CHART I

would be necessary to account for all the bone changes. It is of especial interest to note that the values are altogether dissimilar from those seen in primary hyperparathyroidism (see Table I and Chart I). In the latter condition the calcium and phosphorus losses are all in the urine and of course are much greater than any such changes in this patient. If one hypothesizes that the hormone acts on bone and causes absorption of calcium and phosphorus from bone which is subsequently excreted, then in the patient under question one is at a loss to explain the ultimate disposal of the absorbed calcium and phosphorus. The increased excretion in the feces was not large enough. The possibility that all the absorbed calcium was being redeposited in the soft tissues (*cf.* calcium deposits around joints) seems unlikely from a quantitative point of view. The same argument would hold for the acidosis theory, where again one would expect increased resorption of calcium and phosphorus and excretion somewhere. This patient, on a low-calcium diet, just was not losing very significant amounts of calcium and phosphorus from the body. The findings were more consistent with the other hypothesis—an inability to absorb calcium from the gastro-intestinal tract due to phosphate excretion. The lack of any marked abnormalities would then be apparent. Obviously, in any disorder in which lack of absorption is an important factor, a regime which gives almost nothing to absorb is not very propitious to bring out the abnormality.

On the whole, therefore, the findings seem at least consistent with the possibility that the decalcification was due to a lack of absorption of calcium from the intestinal tract with a slightly increased resorption from bone due to the acidosis. The metabolic data do not favor the theory that the bone changes are the result of the secondary hyperparathyroidism. The mechanism, after all, may be quite analogous to that with which Jaffe, Bodansky and Chandler (11) produced osteitis fibrosa in dogs. These investigators produced changes similar to those seen in experimental hyperparathyroidism by using a low calcium diet plus ammonium chloride to produce an acidosis. There the question must be left until new data are obtained. The bone disease is indistinguishable from that seen in hyperparathyroidism; a secondary hyperparathyroidism was present; but that the bone disease was directly due to the parathyroid hormone remains a question.

(D) CAUSE OF CALCIUM DEPOSITS IN SOFT TISSUES

The authors are indebted to Dr. Franklin C. McLean for a possible explanation of the calcium deposits around the joints (15). He pointed out that the situation was not unlike that which is present when phosphate is injected intravenously into animals. This leads to the formation of a colloidal, non-diffusible calcium phosphate complex, which is quickly removed from the circulation (16). The phosphate retention in the condition under discussion should predispose to the formation of this complex and the calcium deposits may represent its ultimate disposal.

In Table II the results of the chemical analyses of the calcium deposits in the aorta and in the neighborhood of the joints are given. It will be seen that the material compares almost exactly with $Ca_3(PO_4)_2$.

TABLE II

Chemical analyses of calcium deposits around joints and in aorta as compared with $Ca_3(PO_4)_2$

	PER CENT ASH	PER CENT Ca IN ASH	PER CENT P IN ASH	RATIO Ca:P
Deposit in aorta	40.4	35.0	18.7	1.87
Deposit around joint	42.0	34.3	19.4	1.77
$Ca_3(PO_4)_2$		38.7	20.0	1.94

(E) RENAL OSTEITIS FIBROSA GENERALISATA WITH SECONDARY HYPERPARATHYROIDISM VS. PRIMARY HYPERPARATHYROIDISM WITH OSTEITIS FIBROSA GENERALISATA AND SECONDARY RENAL DISEASE

It is obvious that the disease under discussion has many features in common with primary hyperparathyroidism, although these features are arrived at in very dissimilar ways. In any one patient the differential diagnosis might present certain difficulties.

At the autopsy table the finding of only one parathyroid tumor associated with renal changes makes it quite certain that the renal condition did not cause the parathyroid changes or else all the parathyroid tissue would have been involved. On this basis MacCallum's (17) case of nephritis with one parathyroid tumor was interpreted by Albright, Baird, Cope, and Bloomberg (8) as a case of primary hyperparathyroidism. Shelling and Remsen (2), however, although they called attention to the fact that only one gland was involved, considered this case an example of hyperplasia secondary to renal disease.

Shelling and Remsen (2), in discussing this differential diagnosis, make much of the chronology of the symptoms. They state: "In hyperparathyroidism the changes in the skeleton antedate the renal symptoms." This is not true in many instances. Thus, in 35 cases of hyperparathyroidism at the Massachusetts General Hospital proved by operation, 12 had no x-ray evidence of bone disease and no bone symptoms but did have renal symptoms. Even more patients with renal symptoms had no bone symptoms. If one continues to wait for bone symptoms before making a diagnosis of hyperparathyroidism, many people will needlessly die of hyperparathyroid renal disease.

The next question is whether at the time of the clinical examination there is not some finding which would differentiate the two diseases. Shelling and Remsen state that in both there may be "a slightly decreased, normal, or even increased concentration of calcium in the serum—the latter, the usual finding in uncomplicated cases of hyperparathyroidism, may occur in renal rickets, as in the cases described by Parsons (19), Duken (20) and Lightwood (21)." Now the usual finding in patients with chronic renal insufficiency and phosphate retention is a slightly low serum calcium value. Certainly most of the cases of undoubted renal rickets have shown normal or low serum calcium values. Before deciding that the serum calcium is of no value in differentiating the diseases in question, it would be well to examine these three reported cases and see how sure one can be that they represent primary renal disease. Obviously, if there is any possibility of their having been cases of primary hyperparathyroidism they cannot be accepted as evidence of the occurrence of a high serum calcium in renal rickets. The question of the accuracy of the calcium determinations must also be considered. If one goes to the original sources this is what one finds:

Parsons (19): One of the five cases reported by this author showed high calcium values in four out of six determinations. This child was sixteen at the time of the report. No past history was given. There being no autopsy, the important question whether the case was one of hyperparathyroidism or of renal rickets is not clear. The case is obviously unsuitable.

Duken (20): This patient of $8\frac{3}{4}$ years unquestionably had primary renal disease (bilateral hydronephrosis). He gave a negative Chvostek sign but a positive Erb sign (C. O. C. was less than 5 ma.). The first serum (?) calcium determination was 10.0 mgs. and the second, a month later, 16 mgs. %. The signs of tetany remained the same. The inorganic phosphorus level rose from 8.2 mgs. % to 9.0 mgs. %. In this patient with evidence of latent tetany and an inorganic phosphorus level which rose slightly rather than fell it would seem wise seriously to question the second serum calcium value.

Lightwood (21): This child was 1 yr. 5 mos. old at the time of the report. One serum calcium value was high. There is nothing given in the very short report upon which one can make a diagnosis. The case is unsuitable for the same reason as that of Parsons.

It would, therefore, appear that a high serum calcium level may still be of value in suggesting primary hyperparathyroidism as opposed to disease in which renal insufficiency is the first step.

(F) PARATHYROID ADENOMA WITH RENAL DISEASE VS. RENAL DISEASE WITH SECONDARY PARATHYROID HYPERPLASIA VS. PRIMARY PARATHYROID HYPERPLASIA WITH RENAL DISEASE

Osteitis fibrosa coupled with kidney insufficiency must be the result of parathyroid disease when the parathyroid pathology is one adenoma and three normal glands (*v.* supra). When the parathyroid pathology is hyperplasia of all parathyroid tissue, the possibility and probability exist that the disease has originated in the kidney. This conclusion would be simple if it were not for the fact that there is another form of hyperplasia of parathyroid tissue, which, while obviously secondary to something, is not secondary to kidney insufficiency and may lead to kidney damage (18). This form of hyperplasia histologically can be easily differentiated from that secondary to kidney damage (see fig. 6). Thus there are three conditions:

(I) Hyperparathyroidism, with osteitis fibrosa and kidney disease as possible sequelae, due to parathyroid adenoma.

(II) Hyperparathyroidism, with osteitis fibrosa and kidney disease as possible sequelae, due to idiopathic parathyroid hyperplasia, which in turn is due to an unknown cause.

(III) Renal insufficiency, which may lead to a compensatory hyperplasia of parathyroid tissue (histologically distinct from that seen in (II)) and osteitis fibrosa.

(G) IS SECONDARY HYPERPARATHYROIDISM BENEFICIAL?

It has been suggested above that the parathyroid hyperplasia is a compensation for the disturbed equilibrium occasioned by phosphate retention resulting from the renal insufficiency. In the absence of the hyperplasia there would probably be greater phosphate retention in the blood with a resulting lowering of the blood calcium level and severe tetany. If these concepts are correct, the hyperplasia would have to be considered beneficial. The one reservation might have to be made that, while helping homeostasis, the parathyroid hyperplasia may lead to bone disease. This reservation would depend on whether it is the parathyroid hormone or the disturbed equilibrium which causes the bone disease (*v.* supra). In any case from a practical point of view the bone changes in the adult would usually be of relatively little importance. The patient here cited had no bone symptoms.

These hypotheses gain support from experience in the clinic. It has been learned at this hospital that one must be much more conservative in resecting parathyroid tumors in patients with impaired renal function because of the danger of intractable tetany (8) (23).

The points of view set forth in this paper, if correct, lead to one important law as regards the treatment of hyperparathyroidism. It may be stated as follows. As a patient with primary hyperparathyroidism develops more and more renal insufficiency, eventually a point will be reached where the amount of renal damage present will require a degree of compensatory hyperparathyroidism equal in amount to the primary hyperparathyroidism present. When this has occurred, it is probably harmful to remove any of the parathyroid tissue; the nearer it is to occurring, the less parathyroid tissue should be removed.

SUMMARY AND CONCLUSIONS

I. The case record and autopsy findings of a patient are reported who had a disease entity which has been termed renal osteitis fibrosa generalisata. Two similar cases are cited. The characteristics of

the disease are longstanding severe renal insufficiency, marked phosphate retention, normal or low serum calcium level, severe acidosis, arteriosclerosis of the Mönckeburg type (medial arteriosclerosis), calcium deposits around joints, and extreme enlargement of all parathyroid glands.

II. The histological bone changes in this disease are indistinguishable from those seen in primary hyperparathyroidism. It is pointed out that the disease is the counterpart in the adult of renal rickets in children; that the latter condition is a misnomer in that the rickets is not rickets but osteitis fibrosa. Therefore, the term renal osteitis fibrosa generalisata is used instead of renal osteomalacia in the interests of accuracy rather than consistency.

III. The parathyroid hyperplasia is thought to be compensatory due to the phosphate retention.

IV. Metabolic studies on this patient while on a low calcium diet showed increased Ca and P excretions in the feces, slightly decreased or even normal excretions in the urine, and only slightly increased total Ca and P excretions as compared with normal individuals. The Ca and P losses from the body were much less than those that occur in primary hyperparathyroidism.

V. It is pointed out that it must not be accepted without question that the bone disease is due to the excess of parathyroid hormone; other possibilities are that it is due to the marked acidosis or to lack of Ca absorption.

VI. The following three conditions are differentiated:

(a) Primary hyperparathyroidism due to a parathyroid adenoma and predisposing the patient to kidney disease.

(b) Primary hyperparathyroidism due to idiopathic parathyroid hyperplasia and predisposing the patient to kidney disease.

(c) Kidney disease causing compensatory parathyroid hyperplasia and osteitis fibrosa generalisata.

VII. In the differential diagnosis between primary hyperparathyroidism (adenoma or idiopathic hyperplasia) leading to bone and kidney disease and kidney disease leading to compensatory parathyroid hyperplasia and bone disease, the following points are stressed:

(a) The presence of a tumor in only one parathyroid gland shows that the disease most certainly started there.

(b) The fact that the first symptoms are renal rather than skeletal

does not prove that the disease originated in the kidneys since many patients with primary hyperparathyroidism develop only renal symptoms and never develop skeletal symptoms.

(c) The serum calcium should be high in primary hyperparathyroidism, normal or low in disease which originates in the kidneys.

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AN ATTEMPT TO CONDITION ADRENALIN HYPERGLYCEMIA[1]

W. HORSLEY GANTT, S. KATZENELBOGEN AND R. B. LOUCKS

From the Pavlovian and Internal Medicine Laboratories of the Phipps Psychiatric Clinic, Johns Hopkins Hospital

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The concept of reflex involves receptor nerve, central connection and efferent nerve (motor or secretory). Pavlov (1) introduced the term "conditioned reflex" to show the relation of acquired reactions (habits, associations) to the inborn, less adaptable reflexes. His researches indicate, in the dog at least, that the cortex is the organ of central connection for the conditioned reflex, whereas the segmental nervous system may be all that is necessary for the functioning of the unconditioned reflex. Thus Pavlov's concept includes (1) a reflex nervous arc, and (2) the cortex. The purpose of our discussion is to throw light on whether, in the face of recent work, we are justified in holding to a rigid interpretation of this concept.

In lower animals a cortex is not essential for learning or acquired reactions (2). Modifiable behavior is well known not only in animals without a cortex, such as ants and other insects, but even in those lower in the scale who have no well formed nervous system, such as infusoria. But the fact that a cortex is not necessary for learning (behavior modifiable by experience) is not opposed to the performance of this function in the cortex of the higher animals, for in them specialization is the rule; in the lower animals many functions are performed by a single undifferentiated tissue, whereas in the more highly developed animals some of these functions are relegated to specially differentiated tissues.

Our problem therefore confines itself to the higher vertebrates—in whom Pavlov believed that the cortex is wholly responsible for the modification of behavior by experience. In contradiction to this

[1] Read at the XVth International Physiological Congress, Leningrad, August, 1935.

view, on the other hand, some recent work of Zeliony (3) and Culler (3a), would indicate that animals deprived of a cortex may elaborate new associations; and secondly, the investigations of Metalnikov (4), Bykov (5) and others point out that a number of reactions which derive no direct nerve control from the cortex can be conditioned. Among these are the secretion of urine,[2] the contractions of the spleen (Bykov), and such biochemical phenomena as leucocytosis and the development of immune bodies. Dolin of Leningrad claims to have obtained a hyperglycemia during hypnosis to the suggestion "You have drunk a glass of sugared water" (personal communication).

If such varying reactions, some of which are entirely independent of the voluntary nervous system, can occur in the higher animals, it is reasonable to assume that other biochemical reactions can be acquired or modified by the experience of the central nervous system, (although we feel that the work on conditioned leucocytosis, immunity, etc., is as yet unconfirmed). Our present paper represents an effort to delimit in the higher organisms reactions capable of being modified.

In order to test the general hypothesis, whether reactions which do not involve "consciousness" and are apparently on a non-neural level can be modified by the experience of the individual ("taught," or conditioned) we chose a response that is easily produced, lends itself to quantitative measurement, and is independent of the central nervous system—the rise of blood sugar after the injection of adrenalin. Although the mechanism of adrenalin hyperglycemia is not exactly understood, the generally accepted view is that adrenalin stimulates breakdown of muscle and liver glycogen into glucose, and that it may also prevent utilization of glucose by the individual cells. Nevertheless, experiments with such an internal secretion should be important not only for the general hypothesis, but also in endocrine therapy, to show whether we may expect any modification from usage, similar to the conditioning of sleep by morphine when saline is substituted for the drug.

[2] Bykov claims to have shown that urine secretion has a double control, through nerves and also through the hypophysis, so that a conditioned secretion cannot be obtained in a kidney deprived of nerves when the hypophysis has been removed: thus this response is under a neuro-chemical control (personal communication).

ATTEMPTS TO CONDITION HYPERGLYCEMIA IN DOGS

Experimental procedure: The experiments were carried out in 7 dogs which remained fasting over-night; they were brought down six times a week from their paddocks to the experimental room; each dog in turn was tethered to the top of a table which always occupied the same position in the room. As quickly as possible, the experimenter injected adrenalin chloride 1:1000 into the vein of the foreleg. Ten minutes from the time of injection, the dog was taken from the table and tied in another part of the room. When the last dog had been removed from the table, they were all returned to their paddocks.

Adrenalin was the unconditioned stimulus; the unconditioned reaction was the rise of the dextrose content of the blood. (The adrenalin may be thought of as analogous to the morphine in the experiments of Kleitman and Crisler (6), or, more roughly, as similar to a faradic shock at the foot of the animal, leading to the unconditional reflex, i.e., a withdrawal of the limb.) The conditioned signals consisted of various stimuli, tactile, proprioceptive and others, arising from the procedure of tying the dog upon the table, the piercing of his tissues with the hypodermic needle, and the introduction of fluid (adrenalin or saline). While this complex of stimuli might, at first thought, seem somewhat less potent than the bell or flashing light used in the more common routine, in which food is the unconditioned stimulus, the experiments of Crisler, Kleitman, Collins, and Tatum (6) show that such a procedure is adequate. However, to provide what from the formal standpoint would appear to be a more clearcut conditioned signal, a facilitating auditory element, a buzzer, was introduced into the routine beginning with the third week of the training. The buzzer was started at the instant of injection and was run continuously for ten minutes in order to provide for an overlapping of conditioned signal and unconditioned reflex as is ordinarily done. Dogs waiting their turn to be injected were placed in a sound-shielded chamber so that the only time they heard the buzzer was during the ten-minute interval they were on the table following the injection. On certain test days, about once a week, isotonic salt solution was injected instead of adrenalin, the buzzer and other elements of the stimulus-complex being kept as similar as possible to what they were on days when adrenalin was injected.

The unconditioned stimulus, adrenalin, was injected 104, 107, 103 times, respectively, into each of three dogs over a five-month period. In 4 experiments the drug was given intramuscularly, in 8, subcutaneously, and in the remaining 270, intravenously, to avoid pain and injury of tissues. Adrenalin was injected in approximately 85 per cent of the periods, isotonic salt solution being used the rest of the time to test for the presence of a conditional hyperglycemia. For approximately the first half of the training the dogs were given doses of 0.5 c.c. of 1:1000 Parke Davis adrenalin chlorid. A dosage of twice this amount was employed during the latter half of the training. Preliminary analyses for the dextrose content of blood, obtained from the veins of the ears of fasting dogs at various intervals after intravenous adrenalin injection, showed marked rises, if not the peaks of the glycemia, from 8 to 25 minutes after injection. At these intervals the content of dextrose in the blood was determined in 23 experiments after intravenous adrenalin and in 43 experiments after intravenous saline injections. From the values obtained subsequently to the injection of adrenalin there was seen in each case an increase in the level of the blood sugar even though the changes were not great—averaging 21.4 mg. per 100 c.c. In contrast to the consistent trend of the changes in blood sugar subsequent to the injection of adrenalin, the tests after saline injections showed a rise in the sugar level of 10 points or more in only 8 of the 46 determinations and a decrease of 10 points or more in 2 instances (a mean rise of 2.9 mg. per 100 c.c.). (See Table I.) It is evident that there is a definite difference between the average change in blood sugar concentration following the injections of adrenalin as compared with changes in blood sugar after saline injections.

ATTEMPTS TO CONDITION HYPERGLYCEMIA IN RABBITS

It is conceivable that the failure to demonstrate a clearcut and unequivocal conditional response in dogs was due, in part, to the fact that the adrenalin itself elicited such minimal rises in the blood sugar level. Accordingly, the attempt was made to establish a conditional hyperglycemia in rabbits upon the basis of subcutaneous injections of adrenalin.

Experimental procedure: 256 experiments were performed in four rabbits which were run simultaneously. The routine differed in

certain respects from that for the dogs. The rabbits were brought into an experimental room next to their cages and tied on their backs, on adjacent boards, each rabbit occupying the same respective position every day. Adrenalin, or on certain test days isotonic salt solution, was injected subcutaneously in the abdominal region, the experimenter going from one animal to the next as quickly as possible. A buzzer was then started and continued for thirty minutes, after which the rabbits were returned to their cages. In both adrenalin and saline experiments the experimental conditions, including the

TABLE I

Attempts to Condition Hyperglycemia in Three Dogs and Four Rabbits

	DOGS		RABBITS	
	Adrenalin	Saline	Adrenalin	Saline
Number of injections	282	45	229	27
Number of experiments in which blood sugar was determined before and after injection	23	43	15	27
Time after injection of taking blood sample for sugar determination, minutes	8–25	8–25	28–49	28–49
Change in blood sugar following injection, mg. per 100 c.c.	+10 to +163	−11 to +24	+28 to +136	−22 to +61
Number of experiments showing increase in blood sugar.	20 (87%)	10 (23.3%)	14 (93%)	7 (26%)
Average change in blood sugar following injection, mg. per 100 c.c.	+21.4	+2.9	+82.2	+0.4

intensity of the buzzer, were identical. Of the four rabbits employed in the experiment, one was subjected to 21 experimental periods—four test periods wherein saline was injected, and seventeen periods of adrenalin injection. The other three animals were given 50 or more injections each on separate days, lasting over a period of about two months. Two of these three animals were then given a routine of intensive training in which they received several adrenalin injections per day until they had each had a total of 84 training periods.

Results (Table I): Out of the 15 tests for blood sugar after the

injection of adrenalin, there was an elevation of the glycemia above its pre-adrenalin level in 14 experiments (93 per cent) of the cases: the increase ranging between 28 and 136 mg. per 100 c.c. of blood.

Out of the 27 *conditioned* saline experiments, the changes between the fasting blood sugar and the blood sugar after injection of saline varied from −22 to +61 mg. per 100 c.c. of blood; an increase of the glycemia after the saline injection was observed in only 7 experiments (26 per cent); there was often a decrease after the saline; the average increase was only 0.4 mg. per 100 c.c. There is thus a definite lack of evidence for a conditional hyperglycemia in these data. Nor did the two animals that were given the additional intensive training show any indication of a conditional hyperglycemia.

Tolerance: In the experiments on both dogs and rabbits it was found that there was a tendency for the blood sugar response to diminish with successive injections of adrenalin. For example, in the case of *dog 1* the average rise in blood sugar following the first and second injections of 0.5 c.c. of 1:1000 adrenalin solution was 41 mg. per 100 c.c. After the 30th and 60th injections the average increase in blood sugar was only 12 mg. per 100 c.c., in spite of the fact that the adrenalin dosage was twice as large—1.0 c.c. of 1:1000 dilution. In the case of *dog 2* the first and second injections of 0.5 c.c. of 1:1000 adrenalin were followed by an average increase in blood sugar of 27 mg. per 100 c.c., whereas the 30th and 60th injections of twice the dose were followed by an average rise of only 19 mg. per 100 c.c. In *rabbits* the apparent tolerance was less striking: the average rise in blood sugar following the first injection of 0.5 c.c. of 1:1000 adrenalin was 99 mg. per 100 c.c. while the average rise following the 27th to the 55th injections of the same dose was 63 mg. per 100 c.c.

DISCUSSION

In evaluating our results, it is necessary to bear in mind the lability of the blood sugar concentration under various conditions. The comparative study of the results obtained in the unconditioned (adrenalin) and the conditioned (saline) experiments shows, however, such marked differences both in the number of experiments with a hyperglycemia and in the intensity of the hyperglycemia when it was present, that we feel justified in considering the conditioned saline experi-

ments as negative. *In using adrenalin as the unconditioned stimulus in both dogs and rabbits we failed to induce conditioned hyperglycemia.*

The routine procedure used in our experiments was favorable for conditioning, and equivalent to the procedure used in the experiments in which conditioned salivation was obtained by the injection of morphine. The number of repetitions of buzzer and intravenous injections of adrenalin for both dogs and rabbits was certainly sufficient, over 100 times to two dogs and 85 times to two of the rabbits. It greatly outnumbers the 12 to 15 trials reported by Metalnikov (4) in his study of conditioned immunity in rabbits and the 21 trials used, respectively, by Godchikov and Barykina and by Ostrovskaya (7) in their reports of conditioned leucocytosis in guinea-pigs.

TABLE II

Blood Sugar in Milligrams per 100 c.c. Before and After Injection of 1 c.c. Isotonic Salt Solution

DOG	BEFORE	AFTER				
Curley	90	6 min. 91	15 min. 93	25 min. 90	36 min. 93	45 min. 93
Belka	84	6 min. 73	11 min. 73	22 min. 74	31 min. 74	
Collie	81	10 min. 82	22 min. 77	29 min. 78	38 min. 80	

Another objection that might be raised is that in taking but one sample of blood subsequent to the injection of saline the peak of the hyperglycemia might be missed—the conditional response beginning at a longer latent period than the direct response to injected adrenalin. Repeated checks made in both rabbits and dogs failed to substantiate this view. For example, values obtained at the conclusion of the experiments with the dogs were as follows (*cf.* Table II).

Finally, the analyses of glucose were done on specimens of blood obtained at the same intervals after both adrenalin and saline injections. Preliminary glucose determinations in blood samples obtained at such intervals after adrenalin injection showed marked hyperglycemia.

The fact that repeated doses of adrenalin given to patients become somewhat less effective might lead one to inquire whether or not the unconditioned stimulus was adequate or potent throughout the experiment. There is evidence, particularly in the dogs, that the animals developed a tolerance for the drug. We as well as others (Eadie) have observed that subcutaneous injections of adrenalin have a much greater effect on the blood sugar level than do the intravenous doses. One cubic centimeter of 1:1000 adrenalin chloride injected intravenously produced a relatively slight rise in blood sugar in the dogs toward the end of the experiments. This unconditioned rise was so small that it seemed possible that a small conditioned hyperglycemia might be difficult to demonstrate, owing to the obscuring of slight increases by chance variations. Accordingly, the experiments were continued using rabbits in which there was but slight evidence of tolerance. Whether or not the difference in the method of injection (intravenous in dogs, subcutaneous in rabbits) accounts for this we cannot say. The loss of weight in some of the dogs with the consequent decreased storage of glycogen might account for a part of the apparent tolerance (Cannon—personal communication).

The results of Hans Haüsler from Graz, reported in the discussion of our data at the XV International Physiological Congress in Leningrad, agree with ours—*that non-neural conditioning in the higher animals cannot be obtained*. He saw no conditioned hyperglycemia from the injection of 1 c.c. adrenalin per kilogram, nor a conditioned hypoglycemia from the injection of insulin in dogs, nor did he get a conditioned fever from the use of beta-tetra-hydronaphthalamin.

We wish to emphasize the importance of the origin of the hyperglycemia that is being conditioned. The hyperglycemia accompanying a central psychobiological state might become conditioned as a component of this state. The same is true of salivary or gastric secretion—it can be conditioned only when it is a component of a central state, such as nausea, food excitation. Thus one must think of the origin and meaning of the reaction as well as the reaction itself when he speaks of a "conditioned reflex." The hyperglycemia of fear, as shown in Cannon's work (10) is an example of such a central state of excitation. But the procedure in our experiments was not sufficient to cause such a hyperglycemia, as shown by the following experiments.

Four rabbits tied on their backs were given a strong electric shock on the leg for five minutes, sufficient to make them squeal, but there followed no increase in blood sugar concentration (experiments of R. B. Loucks). Furthermore, the state of cortical or emotional excitation caused by the adrenalin probably does not come until after the initiation of the process responsible for the hyperglycemia, and thus would be ineffective in elaborating hyperglycemia; for as Pavlov has shown, when the conditioned signal follows instead of precedes the unconditioned reflex, the former can hardly develop the power of evoking any conditioned reflex.

Adrenalin evidently regulates the carbohydrate metabolism essentially through direct action on body tissues and not through provoking a psychobiological state (9) which would cause stimulation of the subcortical vegetative centers and of the whole chromaffin system. This view explains our failure to provoke conditioned hyperglycemia when adrenalin is used as the unconditioned stimulus.

Also, comparing our experiments with those using centrally acting (morphine) and peripherally acting drugs (pilocarpine, atropine) to affect salivation, and the failure to obtain a conditioned salivary reflex in the latter, it appears that the action of adrenalin in producing hyperglycemia is peripheral, which accords with its ability to cause a rise of blood sugar in the perfused liver (13), or when injected into decerebrate and decapitated cats (14, 15), and also after removal of the sympathetics (11).

In our experiments we obtained conditioning of reactions other than hyperglycemia. The intravenous injection of adrenalin frequently produced dyspnea, retching, blanching of the tongue and salivation. These may be considered as signs of a central emotional state (nausea) of which salivation is a component. On test days when saline was injected instead of adrenalin, in many more cases than chance can account for, saliva dripped from the dog's mouth at the instant the hypodermic needle pierced the skin. On this ground, of central rather than peripheral action, the salivation is easily explained. Some of the dogs also developed (conditioned?) tics, notably muscular tremors in the legs, and in one dog a movement in the hind leg suggesting the scratch reflex. These would appear when the dog was placed on the table where the adrenalin (or saline) was injected.

How may our failure to obtain conditioned hyperglycemia be correlated with the ordinary conditioned reflex experiments, or with such extreme examples as those of Bykov's experiments (5) in which he obtained conditioned contraction of the spleen to a metronome used for 3 to 6 seconds at the time of injection of adrenalin and also a conditioned carbon dioxide and oxygen exchange as well as a conditioned respiratory quotient with adrenalin as the unconditioned stimulus (12); and furthermore, how may the failure of hyperglycemia be correlated with our own conditioning of adrenalin dyspnea, and with the development of tics?

All these results agree with the theory—the *effects of adrenalin which have a cortical representation through afferent fibers (even though enteroceptive) as well as an efferent control, can be conditioned*, while those without such adequate representation or efferent control fail.

The second corollary of these experiments is that *we should speak of conditioning specific reactions* rather than employ the loose and vague expression—a "conditioned reflex to a drug." The conditioned response to an agent may be selective, consisting only of part of the original unconditioned action, thus varying from the latter *qualitatively* as well as quantitatively. Hence conditioned responses may differ considerably from the original reactions on the basis of which they were formed. Conditioning is a filtering process rather than a duplication *in toto*.

Thirdly, from the fact that some of the effects of adrenalin can be conditioned, it is necessary to remember that one and the same reaction may be conditioned at one time and not at another. Thus it is understandable why the hyperglycemia accompanying a central excitation such as fear might be conditioned to the stimulus for the central state, albeit the final mechanism of the hyperglycemic production is through the action of adrenalin and is non-neural; for the liberation of adrenalin is a result of the central state. But where adrenalin is introduced artificially, the difference is analogous to that which exists between the production of salivation *peripherally* (by the injection of pilocarpin which cannot be conditioned) and the production of salivation *centrally* (by the eating of food); in the former, there is no central excitation, whereas in the latter instance the salivation is preceded by and is an expression of the central excitation.

SUMMARY

In attempts to condition hyperglycemia in dogs and rabbits, using adrenalin as the unconditioned stimulus, and saline injections and other signals as conditioned stimuli, the results were negative. The fact that some of the other effects of adrenalin became conditioned in our experiments lead us to conclude that in the higher animals a psychobiological state generally underlies the conditioning process.[3] A tolerance, so far as blood sugar increase was concerned, developed in the dogs.[4]

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THE OCCURRENCE OF CONSTITUTIONAL REACTIONS IN THE TREATMENT OF HAY FEVER AND ASTHMA: ANALYSIS OF THE CAUSATIVE FACTORS

FRANK F. FURSTENBERG, M.D. AND LESLIE N. GAY, M.D.

From the Protein Clinic of the Medical Dispensary of the Johns Hopkins Hospital

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In recent years, there has been a great increase in the use of pollen extracts for the treatment of hay fever and pollen asthma, and the commercial houses have done their utmost to popularize this form of treatment. Today, extracts of dusts and danders are available for the treatment of atopic asthma and perennial rhinitis, and allergic diseases and their treatment form an increasingly important part of the daily work of the general practitioner.

STATEMENT OF PROBLEM

At such a time, it may not be amiss to evaluate the dangers of injection therapy with these protein extracts; and, in the present report, the constitutional reactions that sometimes follow injections of pollen extract or other air-borne allergens will be dealt with. The gravity of the reaction to the patient, its incidence, and the means of prevention will be discussed. The material analyzed has been derived from the cases treated during the years 1930 to 1936 in the Protein Clinic of the Johns Hopkins Hospital and in private practice.

The Protein Clinic is the teaching clinic for allergy in the medical school. In it patients may be given injections by as many as fifteen different physicians during the course of a year. In our private practice, however, no patient has been treated by more than two physicians.

The present paper will not concern itself with the dangers of diagnostic skin testing with the various allergens such as pollens, dusts, danders and foods. Deaths from intradermal tests have been reported by Lamson (1), Cooke (2) and Baagoe (3). Unpublished fatal cases are well known to those engaged in the treatment of allergy. Scratch tests are not without danger. Intracutaneous tests cannot

be performed by the inexperienced physician without real jeopardy to the patient. But how dangerous is injection therapy?

Summary of literature referring to constitutional reactions in treatment. Dunbar (4), 1903, using large amounts of pollen extracts in the treatment for grass hay fever, encountered many severe reactions. The reactions were so severe that he discontinued their use and, instead, treated his patients with pollantin (immune horse serum). It was L. Noon (5), in England, who first began to use graduated doses of timothy extract for the preseasonal treatment of grass hay fever in the summer of 1910. In his original publication, he did not report any constitutional symptoms from these injections. Freeman (6) carried on Noon's work and in September 1911 reported a study of 20 cases of grass hay fever treated with timothy pollen extract. He says: "If the dose were increased markedly, one might produce, even in midwinter, such unpleasant things as swelling, pain and urticaria at the site of the inoculation, a general malaise and all the nose and throat symptoms of a thorough attack of hay fever." He gauged the dosage by ophthalmoreaction rather than by the present day skin reaction but makes the interesting statement: "Owing to the nature of hay fever there is no danger to life and only temporary danger to health by inoculating 'blindly'."

To George H. Clowes (7), in 1913, belongs the credit of reporting the first constitutional reaction in America. He precipitated hay fever with dizziness and generalized discomfort by the injection of 1.0 c.c. of a 1:50,000 ragweed extract.

After him, in 1915, Oppenheimer and Gottlieb (8) gave us a picture of constitutional reactions to pollen extract. Rackemann (9), in 1917, reported the precipitation of asthma, 2 minutes after an injection of horse-hair dander in a sensitive female asthmatic. In this case, he noticed some blood in the syringe when injecting. He mentioned another case in which an overdose of extract caused asthma and then generalized urticaria and angioneurotic edema lasting for five days.

Cooke and Vander Veer (10), in 1916, in an admirable paper on the subject of hay fever reported the first statistical study on the constitutional reactions in treatment. In a series of 339 such patients they noted that 29% of the patients suffered reactions and 3.75% of the injections were followed by constitutional symptoms. Later, in 1922, Cooke (2) discussed the entire subject of testing and injecting with protein extracts in regard to the dangers involved, and presented a factual study of his then extensive experience. In this paper, he said that the reaction might be immediate or delayed—as long as five days after injection. He noted the usual symptoms of an overdose, such as coryzea, asthma, urticaria, erythema, pruritus, edema and cough, but also mentioned the less frequent symptoms such as glandular enlargement, headache, fever, nausea, diarrhea, acute abdominal pain, dysmenorrhea, syncope and even cardiac collapse. Cooke outlined the causes and treatment of these constitutional reactions. He stated that intravenous or intralymphatic administration, individual sensitivity, overdosage

due to too potent extracts or to too frequent injections, and multiple sensitivity with exposure, were among the causes. Epinephrine hypodermatically and a tourniquet applied above the site of injection was his main treatment for the reaction when once precipitated.

Since this excellent exposition of the subject, little has been added to our knowledge regarding the causes and treatment of an overdose of pollen extract. The incidence of reactions has, however, steadily decreased. Vander Veer (11) and his associates, in 1927, and Markow and Spain (12), in 1930, stated that in their series of hay fever patients, only about 10% suffered from any constitutional symptoms following injection therapy, and that less than one out of 100 injections was followed by such a reaction. With the advent of perennial treatment for hay fever, some observers felt that an objection to this type of treatment was to be found in an increase in constitutional reactions. Figley (13), however, reported that 65 cases so treated with only 10 reactions in more than 2000 injections gave an incidence of only 0.5%. Unger (14) also believes that reactions do not increase with perennial treatment, though Thommen's (15) results and the even more recent report of Peshkin (16) would indicate the contrary.

"Rush inoculation" introduced by Freeman (17), and "rapid hyposensitization" used in selected cases by Waldbott and Asher (18) (that is, 3 to 6 or even more injections of pollen extract a day) have been followed by many constitutional reactions. Intravenous therapy has been used by Lichtenstein (19) in the treatment of ragweed hay fever, but the numerous constitutional reactions would arouse apprehension in most physicians engaged in this field.

The method of administration of the extract and its relation to reactions has been discussed in the literature. Phillips (20) is a proponent of intracutaneous administration, Duke (21) believes in subcuticular administration, while Gay (22) uses subcutaneous injections. Following several severe reactions in 1929, Duke devised the following method to prevent too rapid absorption of pollen: (1) He places a tourniquet above the site of injection, removes and replaces it for 15 minutes after injection; (2) he mixes epinephrine and ephedrine with the extract to slow the rate of absorption; (3) he mixes physiological saline with all doses of extract to bring them to a constant volume; (4) and introduces .01 cc. of the extract subcuticularly just before injection. Rice (23) and Insley (24) propose similar methods. Waldbott (25, 26, 27) has, perhaps, written more than any other recent author on the subject of systemic reactions from pollen injection. He has emphasized especially the immediate intravenous type of reaction which endangers the life of the patient; also, what he calls the back-seepage reaction due to the "puncture of a vein and backseepage into the blood stream." In the first type, he states that the reaction occurs immediately, and that, in the second, 1 to 5 minutes elapse before the symptoms appear. He suggests Duke's method of administration, or advises that the injection be given subcutaneously in the extensor surface of the forearm. The plunger should be retracted repeatedly so that any blood in the syringe can be detected and the site observed after injection for the appearance of blood. Finally, tight pressure should be applied over the injected area as a precaution.

Administration of extracts (complete procedure). Our own method of administration of the various extracts has been relatively simple. We use 5% extracts made with Coca's solution.[1] In treatment, we use only 1 cc. tuberculin syringes with tightly fitting glass plungers. The needle is a 25 gauge, ½ inch. The extract is always given deep-subcutaneously, in the outer aspect of the mid-upper arm. Before injection, the plunger is always retracted to avoid injection into a blood vessel and it is customary to retract the plunger again after partial injection of the extract. Pressure is applied momentarily after injection, and the patient remains in the office for 15 minutes. In the clinic, patients treated preseasonally are given injections as often as three times a week; in the office, occasionally, more frequently. Treatment of the pollen-sensitive group is coseasonal, preseasonal, or perennial, as indicated.

If a patient comes to the clinic in the middle of a pollen season, coseasonal treatment is given. From experience, it has been learned that small and frequent doses of the specific extract will give relief. The dose, 0.1 cc. of a 1:1000 dilution, is injected subcutaneously every 24 to 72 hours during the season. The interval is lengthened as the patient's symptoms are relieved, but the amount injected is constant.

The ideal time to begin the treatment, however, is at least two months before the usual onset of symptoms. The concentrated pollen extract is diluted 1:2, 1:10, 1:100, 1:1000, and 1:10,000. The initial dose depends on the degree of sensitivity of the patient to the specific pollen determined by the intradermal test. Treatment should be given every three to seven days in graduated doses, and the maximal dose should be attained before the pollen appears in the air.

1. *Dilution—1:10,000*
   Six doses
   0.1 cc. to 0.9 cc.

2. *Dilution—1:1000*
   Six doses
   0.1 cc. to 0.9 cc.

3. *Dilution—1:100*
   Nine doses
   0.1 cc. to 0.9 cc.

4. *Dilution—1:10*
   Ten doses
   0.05 cc. to 0.9 cc.

5. *Dilution—1:2*
   Six doses
   0.05 cc. to 0.5 cc.

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[1] Our extracts are made by adding 100 cc. of Coca's solution to 5 grams of ether-extracted dry pollen. The total nitrogen is then adjusted to 0.5 milligram per cubic centimeter. The protein nitrogen varies between 0.24 and 0.3 milligram per cubic centimeter.

Coca's Solution contains: 2.8 gms. Sodium Bicarbonate.
5.0 gms. Sodium Chloride.
4.0 cc. Phenol (95%).
to 1000 cc. Distilled Water.

After the maximal dose has been given to the patient, this dose is continued at weekly intervals throughout the pollen season.

The perennial method begins when the pollen season ends. After a patient has reached the maximal dose of 0.5 cc. of 1:2 dilution, this amount is given every two weeks throughout the year and only after there has been absolute relief of symptoms for three years should all treatment be discontinued and give place to a trial season without treatment.

TYPE OF CONSTITUTIONAL REACTION STUDIED

Recognition of a constitutional reaction is not difficult. Cooke's description of the symptoms and signs is clear. The physician treating allergic patients should be aware of the minor warning symptoms and signs, but the present study concerns itself with the graver reactions, that is, with those requiring epinephrine as treatment, and a drop in dosage in the following injections. When there has been merely some subjective itching and the physician has proceeded with the subsequent and larger dose, the cases have not been included in this study. Neither have those cases been recorded in which there was a supposed mild exacerbation of hay-fever symptoms during the season following injection of extract. In these instances, there was no objective control and such reports would have depended upon subjective manifestations of the patients. Nor have we included the rare instances of asthma or other allergic manifestations occurring later than 12 hours after injection. The symptoms and signs of the constitutional reactions with which this paper deals are: widespread or generalized pruritus, angioneurotic oedema, hay-fever symptoms out of season, asthma, cough, generalized erythema, nervousness, palpitation, and tachycardia. These symptoms have required immediate epinephrine and subsequently a decrease in the dosage of pollen extract.

RESULTS

Included in this study are 627 patients from the clinic and 280 from private practice. Of these 907 patients 45, or 4.9 per cent, had major constitutional reactions in the six-year period. To the entire group of patients 43,771 injections were given, with 87 constitutional reactions. This means that 1 in 500 or 0.2 per cent of the injections gave rise to a constitutional reaction. The cases have been separately

classified and studied under three headings: (1) Those receiving treatment with one or more of the pollens, from trees, grasses, or ragweed. (2) Those receiving treatment simultaneously with the pollens and any other air-borne factors such as dust, orris root, feathers, horse dander, etc. (3) Those receiving treatment only with air-borne allergens other than pollen.

The pollen group. Of major interest are those reactions that arise in the treatment of the simple hay-fever or pollen asthma. In this group are presented 351 cases from the clinic, with 615, or an average of 1.7 seasons of treatment (see Table 1). The private patients number 177, and received 467 courses, or an average of 3.3 seasons of

TABLE 1

Analysis of constitutional reactions in the pollen sensitive patients

YEAR	PRIVATE PATIENTS 171 patients treated 20 patients had constitutional reactions 11.7% patients had constitutional reactions			DISPENSARY PATIENTS 351 patients treated 21 patients had constitutional reactions 5.9% patients had constitutional reactions		
	Seasons of treatment	Number of injections	Number of reactions	Seasons of treatment	Number of injections	Number of reactions
1930	34	1,097	0	79	1,991	5
1931	52	1,497	0	119	2,624	4
1932	68	2,447	3	123	2,742	6
1933	84	2,688	7	100	2,478	4
1934	102	3,297	3	79	2,091	10
1935	127	3,745	12	115	2,840	21
	467	14,771	25 (0.16%)	615	14,766	50 (0.33%)

treatment in the six years of the study. The number of injections given the clinic patients totals 14,766 or an average per season of 24 injections. The total number of injections given the private patients amounted to 14,771, an average of 31.6 injections per season. In this group, therefore, the private patient received 7.6 more injections per season than the clinic patient.

The number of patients experiencing constitutional reactions in the clinic in the six-year period was 21, or 5.9 per cent. Of the private patients, 20, or 11.7 per cent, suffered major reactions in the same period. The total number of reactions experienced by the 21 clinic patients was 50, or an average of 2.4, while in the 20 private patients

there were only 25 reactions, an average of 1.2. These figures are significant and require interpretation. That only 5.9 per cent of our clinic patients should have had constitutional reactions is due to the fact that many of them do not receive maximal dosage. A good many find it difficult to come to the clinic until symptoms begin, and we have met with very few constitutional reactions in the patients receiving co-seasonal treatment. Of the private patients, 11.7 per cent at one time or another during the course of the treatment, suffered a constitutional reaction. This figure approximates the experience of other observers (Markow and Spain, Vander Veer, *et al.*), and probably represents the basic expectancy of constitutional reactions with our present methods of treatment. Of greater interest is the number of reactions per person. In 21 clinic patients 50 reactions—an average of 2.4—were met with, while in 20 private patients there were 25 reactions—an average of 1.2. No private patient had more than 2 reactions in the 6-year period, while 6 of the clinic patients had 4 reactions and 3 of these suffered from a fifth constitutional reaction in the 1936 season not included in this paper. Of the 21 clinic patients suffering from reactions, 7 had only one reaction, and the remainder, 14 patients, had 43 reactions. The explanation for this lies in the increased number of relatively untrained physicians who treated the patients in the clinic, their lack of personal relationship to the patients, and lack of knowledge of the patients' past treatment, but mainly in the attempt to treat the patients susceptible to reactions in a routine fashion. That no patient in the private group had more than 2 reactions and that 75 per cent of the patients had only 1, though the same solutions and methods of treatment were used, would seem to bear out this explanation.

Examination of the tolerance point, which is the level of dosage above which reactions occur, in the private patients reveals no uniformity. In 16 cases, no real cause for the symptoms of overdosage could be ascertained. Of the 25 reactions, however, 5 occurred after use of the concentrated extracts, and for this reason, in the last year, we have stopped using concentrated extracts in treatment and have substituted a 1:2 mixture with which we hope to be able to reduce the incidence of reactions while maintaining maximal dosage. The too frequent treatment of several private patients may have been re-

sponsible for constitutional reactions, as Levine and Coca (28) have shown that not all the pollen is excreted in 7 days. Four patients given the same large dose, more than 0.5 cc. of a 1:10 dilution (2500 Noon units), at 48-hour intervals, suffered from general reactions. In 5 cases which gave 20 per cent of the reactions, the dose had been increased too rapidly. Certainly we have all sometimes yielded to the temptation to push treatment to optimal dosage and in doing so induced a constitutional reaction. Since there is a real question whether massive doses of pollen extract are more efficacious than moderately large doses, it may be well to increase doses cautiously in the 1:10 dilution (0.1 cc. of a 1:10 dilution = 500 Noon units). Clarke (29), in 1923, and Freeman (30), in 1927, pointed out the dangers of increasing the dose too rapidly. In 2 cases in the 6 years, the first injection of pollen extract caused constitutional symptoms. While we use a modified form of Cooke's classification, or that of Markow and Spain, a large number of the patients were given 0.1 cc. of a 1:1000 extract (5 Noon units), as the first injection. This dose is large enough to cause constitutional symptoms in the rarer hypersensitive patient, and to avoid this one should begin with 0.1 cc. of 1:10,000 extract.

From the reactions of the clinic patient we learn more perhaps, because of the less efficient treatment. It was emphasized that our clinic patients with the liability to constitutional reactions have met with such mishaps with discouraging regularity, and several have had 4 reactions in a period of 6 years. Several of the cases show, with truly dramatic effect, the fact that some patients have a relatively "fixed" tolerance point, as was emphasized by Thommen (31), in 1930, in discussing the fatality reported by Lamson (1).

Case 1. On August 1, 1932, J. E., received 0.5 cc. of a 1:10 mixture of ragweed extract, with a resultant urticaria and asthma in 15 minutes. On July 31, 1933, 0.5 cc. of a 1:10 ragweed extract induced a similar reaction in five minutes; and on July 10, 1935, 0.5 cc. of a 1:10 ragweed extract also caused asthma. On all three occasions, the previous dose had been 0.4 cc. On two occasions, the interval following the previous injection had been 48 hours, and on the third, five days.

Case 2. On July 18, 1934, R. S., received 0.1 cc. of 1:10 ragweed extract and in one hour had a violent reaction. On July 3, 1935, 0.2 cc. of 1:10 extract resulted in a generalized urticaria within 15 minutes. The subsequent dose on

July 6, 1935 was 0.1 cc. of 1:10 dilution and no reaction occurred. However, on July 9, 1935, 0.2 cc. of 1:10 ragweed caused an immediate violent reaction. During 1936, this patient was closely observed as the dose 0.1 cc. of 1:10 extract was approached; but, when given 0.9 cc. of 1:100 dilution, a typical reaction occurred within 45 minutes. In other words, the tolerance of this patient to ragweed lies between 0.9 cc. of 1:100 and 0.2 cc. of 1:10 dilutions.

These two patients are only examples of several others in whom there is a hair-line tolerance point which is relatively "fixed," and who must be treated cautiously. Perhaps one constitutional reaction predisposes to another. Certainly conservative dosage is indicated, once a tolerance point is reached, since we know that attempts to overcome the resistance to higher dosage may result in an explosive general reaction. M. Walzer (32) feels that, when one has induced more than one constitutional reaction at a given level of dosage, one should accept this dosage as the maximum and not attempt to overstep it.

In 11 of the fifty reactions, 22 per cent, concentrated extracts were used. As stated previously, we are now using a 1:2 mixture as our strongest extract. For twenty-seven of the reactions, careful examination does not reveal the probable cause. Curiously enough, in not one instance did the initial dose cause a reaction in the clinic group.

What is more interesting, is the observation that 22 reactions (44 per cent) occurred when the volume of the extract, regardless of strength, was 0.2 cc. or less, and 27 reactions (54 per cent) occurred when the volume was 0.3 cc. or less. The observation that the amount of diluent tempers the speed of absorption has been previously reported by Duke; in his technique of administration of pollen extracts he brings each injection to a constant volume. Duke noted that going from 0.9 cc. of a weaker to 0.1 cc. of a stronger solution was a danger point. This is confirmed by the examination of the reactions in our clinic. The most dangerous point is the increase from 0.9 cc. of a 1:100 solution (450 Noon units) to the next dose of 0.1 cc. of a 1:10 (500 Noon units) and in immediately following doses. Of 50 reactions, 15 (30 per cent) occurred when 0.05 cc. to 0.3 cc. of a 1:10 pollen extract was given.

Pollen and inhalant group. When one examines the constitutional reactions after treatment of that group of individuals sensitive to pollen who also suffer from other air-borne allergy, one finds startlingly

different results as regards reactions. These patients often represent that group of individuals who do not respond to pollen extracts alone, and in whom we have to look for other causes to explain poor clinical results. It is interesting that we have in this group 83 private patients and only 48 from the clinic (table 2). These received a total of 249 seasons of treatment and 6690 injections. Only two patients, 1 private and 1 clinic, suffered from constitutional reactions. Of these two patients, one had 3 and the other had 2 reactions. The case of the private patient can not be explained except on the basis of tolerance, for he was receiving grasses, ragweed, and a mixture of dust, feathers and orris-root. The clinic patient was receiving concen-

TABLE 2

Analysis of constitutional reactions in the pollen-inhalant sensitive patients

YEAR	PRIVATE PATIENTS		DISPENSARY PATIENTS	
	83 patients treated 1 patient had 3 constitutional reactions		48 patients treated 1 patient had 2 constitutional reactions	
	Seasons of treatment	Number of injections	Seasons of treatment	Number of injections
1930	5	122	2	31
1931	4	92	2	77
1932	14	427	6	148
1933	21	636	19	566
1934	35	1,060	27	686
1935	68	1,905	26	740
	147	4,242	82	2,248

trated ragweed extract and 1:5 house dust. Why do reactions occur so infrequently in this group (0.07 per cent of the injections as compared with 0.31 per cent of the pollen-treated clinic group)? Perhaps the answer may be found in the fact that the total volume of the individual injection given to this multiple sensitive group is very seldom below 0.2 cc., and usually much higher, because we usually inject the extracts together.

Inhalant group. Finally, we have studied the group of patients treated with air-borne allergens other than pollen. We have only 26 of these patients from private practice with 47 seasons of treatment and 964 injections (table 3). There are no constitutional reactions to

report among them. From the protein clinic, we report 228 cases, a total of 232 seasons of treatment and 6780 injections. In this group, there were 2 patients who suffered from constitutional reactions, one from 4, and the other from 3. For statistical purposes, we have grouped the private and clinic patients together. Of this group, 0.8 per cent suffered constitutional reactions and 0.09 per cent of these injections caused constitutional reactions. The number of reactions in this group is minimal. This can be explained by the fact that many of these patients represent the problem cases of allergy. Some suffer from severe asthma of doubtful origin, and are given treatment on a

TABLE 3

Analysis of constitutional reactions in the patients sensitive to air-borne allergens other than pollen

YEAR	PRIVATE PATIENTS		DISPENSARY PATIENTS	
	26 patients treated 0 patients had constitutional reactions		228 patients treated 2 patients had 7 constitutional reactions	
	Seasons of treatment	Number of injections	Seasons of treatment	Number of injections
1930	2	41	23	368
1931	2	52	45	960
1932	3	34	51	1,154
1933	4	60	63	1,269
1934	7	174	77	1,660
1935	29	603	64	1,369
	47	964	323	6,780

basis of skin sensitivity when the other approaches have failed. In this group there is also a large number of patients with vaso-motor rhinitis, and in whom the allergic basis is not well established. Then too, these extracts themselves are not so apt to cause symptoms of overdose as the pollen extracts. Finally, many of the patients have symptoms comparable to those of a constitutional reaction when taking therapeutic injections, so that despite careful evaluation certain true constitutional reactions may have been overlooked. We have seen unquestionable reactions from a mixture of dust, orris-root, and feathers, from horse dander and, in the 1936 season, from cotton-seed.

DISCUSSION

From an analysis of the constitutional reactions occurring both in private practice and in the clinic, it would seem that reactions may be expected to occur in any group as long as our present methods of extraction and treatment are used. Careful skilled handling of the individual case should prevent the occurrence of reactions once a tolerance point has been established. Despite the fact that the clinic patient is subjected to the care of many physicians, the number of constitutional reactions at the Johns Hopkins Hospital Protein Clinic compares favorably with the number reported by other observers (table 4). We have seen no grave reactions from our treatment with therapeutic injections in private or in clinic practice. Fortunately we have thus far never met with the so-called intravenous constitutional

TABLE 4

Comparison of contemporary reports

	YEAR	NUMBER OF POLLEN INJECTIONS		NUMBER OF CONSTITUTIONAL REACTIONS	
Vander Veer et al.	1926		14,280		96
Waldbott and Ascher	1932 to 1935		51,036		141
J. H. H. *Clinic*	1930 to 1936	14,776	29,547	50	75
J. H. H. *Private*	1930 to 1936	14,771	29,547	25	75

reaction as reported by Waldbott, nor have we noted his "back-seepage reactions." Undoubtedly these do occur, but with our relatively simple technique of administration they have not occurred. Not more than once or twice a season do we see blood at the site of injection after withdrawal of the needle. In these instances, we do not inject epinephrine, nor apply a tourniquet, but watch the patient carefully for 15 minutes. Perhaps our success in avoiding the graver reactions described by other observers can be ascribed to the use of tight-fitting glass plungers instead of asbestos wrapped plungers which frequently allow leakage, and also to the site of injection, which is deep-subcutaneous in the outer aspect of the upper arm.

Other factors do occasionally play a rôle in the precipitation of constitutional reactions and should be mentioned. Exercise and exposure to heat immediately after injection, as emphasized by Duke;

multiple sensitivity with exposure after injection, as indicated by Walzer (32) and by Waldbott (33), are occasionally the causes of symptoms of overdosage. Levine and Coca's work (28) showing an increase in reagins in some patients, when under treatment, suggests that this may be the specific cause of an occasional constitutional reaction. When changing from old solutions to new extracts, some observers have noted constitutional reactions. It is our custom to decrease the dose for several injections, and by these means we have avoided this cause of reactions. During the late fall of 1934, perennial treatment was instituted in a larger group of pollen-sensitive individuals than had been so treated in previous years. Careful examination of the records of these individuals, in an attempt to explain the increase in constitutional reactions in 1935, has failed.

One wonders how often outright mistakes in the amount of extract given are the cause of constitutional reactions. In a busy clinic or in private practice such reactions will occasionally occur despite any system used to prevent them. During the period of the present study 9 such errors have been recognized; 5 of these, not included in the tables, resulted in constitutional reactions. It is possible that errors in dosage account for some of the reactions included in the tables, but in these instances the error was not discovered. That errors do not account for most of the reactions is borne out by our experience in the clinic pollen-treated group in which 14 of the 21 patients had more than one constitutional reaction.

The most significant causes of reactions and those with which we have been most impressed are as follows: (1) a definite tolerance point in some patients, and (2) reactions resulting from the shift in dosage from a large volume of lesser strength to a much smaller volume in the next stronger dilution. We are certainly of the opinion that many reactions are dependent upon dosage, so that, on the one hand, while Piness' (35) point is well taken—that equally severe reactions have occurred with small as well as large doses of antigen—on the other hand, our study of the clinic pollen-sensitive group emphasizes the fact that the individual susceptible to constitutional reactions suffers from them repeatedly after similar or identical large doses of pollen extract at widespread intervals.

We are fortunate in not having observed the immediate and very

grave *collapse reaction* from treatment. Except for Lamson's case the literature is barren of reports of deaths from therapeutic injections of allergens. That there have been other fatalities is well known, and it is regrettable that these have not been put on record in the literature.

Only a few words are needed to outline the treatment of the constitutional reactions. Intramuscular epinephrine and immediate application of a tourniquet above the site of the injection are still the only means of treatment. There should be one word of warning: Be certain that the epinephrine, which must always be on hand when the patients are being treated, has not deteriorated.

SUMMARY

1. 87 constitutional reactions occurred in 43,771 therapeutic injections of allergens.

2. 11.7 per cent of the private patients and 5.9 per cent of the clinic patients treated with pollen extract have shown constitutional reactions.

3. 0.16 per cent of the injections of private patients treated with pollen extract were followed by constitutional reactions.

4. 0.33 per cent of the injections given clinic patients treated with pollen extract were followed by constitutional reactions.

5. The clinic patient had repeated reactions, as many as 5; the private patient never more than 2.

6. The most important causes of constitutional reactions were the following: (1) Individual tolerance of the patient for a given dose, and (2) Change from a large volume of a weaker extract to a small volume of a stronger extract, in spite of careful methods of standardizing the preparation of extracts.

7. Less important causes were: the use of too concentrated extracts, too frequent injections, too large an increase in dose and too large an initial dose.

8. For half of the constitutional reactions in the clinic group, and for two-thirds of the constitutional reactions of the private patients there was no discoverable cause.

9. Patients receiving pollen and inhalant extracts together have

very few constitutional reactions, less than 2 per cent—0.07 per cent of the injections cause general reactions.

10. Patients receiving only inhalant extracts have even fewer constitutional reactions, less than 1 per cent—0.09 per cent of the injections cause general reactions.

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ON THE PROLONGED COAGULATION TIME SUBSEQUENT TO ANAPHYLACTIC SHOCK

HARRY EAGLE, C. G. JOHNSTON, AND I. S. RAVDIN

From the Departments of Bacteriology and Research Surgery, University of Pennsylvania Medical School, Philadelphia, the Department of Medicine, Johns Hopkins Medical School, Baltimore, and the United States Public Health Service, Washington

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It is a well established observation (1, 2) that, following anaphylactic shock, blood coagulation may be either markedly retarded or completely inhibited. This prolongation of coagulation has been variously ascribed to the transformation of fibrinogen to an insoluble modification (8), a decreased fibrinogen content and decreased thrombin production (7), a decreased prothrombin content (4, 11, 13), an increase in the antithrombic activity of the plasma (9, 13), and a platelet deficiency (5, 9, 10). Wöhlisch (1929, p. 588) concludes, in his extensive review on blood coagulation, that no satisfactory explanation for the non-coagulability of blood after anaphylactic shock has yet been offered.

The following experiments were undertaken in an effort to ascertain the nature of the inhibition. As will appear, the coagulative deficiency in the present series of animals could be ascribed to a marked increase in the antithrombic activity of the plasma; and there was no evidence that any other factor in the coagulation reaction was quantitatively or qualitatively altered.

METHODS AND MATERIALS

Production of shock. The animals used were rabbits and dogs. Guinea-pigs were first tried; but not one of fifteen animals sensitized by the intravenous injection of 0.5 cc. of horse serum, and fatally shocked by the intravenous injection of 0.5 cc. horse serum sixteen to eighteen days later, showed a significant prolongation of the coagulation time. Such prolongation was, however, regularly observed in

rabbits and dogs. The rabbits were sensitized by the intravenous injection of 0.5 to 0.75 cc. of horse serum three times weekly for a total of six to eight injections; and shock was induced by the intravenous injection of 3 cc. of horse serum six to ten days after the last injection. The symptoms consisted largely of increased respiratory rate and weakness. Fifteen dogs were sensitized by the injection of 3 cc. of horse serum on each of three successive days, the first two injections intravenous and the last subcutaneous. Three weeks later, the animals were shocked by the intravenous injection of 15 to 20 cc. of serum. In eleven of the fifteen, shock was very severe, consisting of respiratory distress, vomiting, urination, and defecation. Nine of these eleven dogs died within one to two hours after the shocking injection; however, the repeated cardiac punctures for the withdrawal of blood samples, with subsequent hemorrhage into the pericardial sac, may have been a contributory cause of death. Of the four dogs which did not develop shock after the injection of horse serum, three showed no retardation of coagulation, and the antithrombic activity of their plasma was found to be correspondingly normal. They thus served as fortuitous controls.[1]

Thrombin and fibrinogen were prepared by the method previously described (3) (3a).

The time required for the formation in a small test tube of a clot which could be inverted without spilling was the arbitrary *coagulation time.*

Fibrinogen was determined by three methods: (a) One cubic centimeter of 1:2 plasma was heated at 56°C. for 15 minutes. The coagulated protein was washed twice with 2 cc. of 0.85 per cent salt solution. (b) One cubic centimeter of 1:2 plasma was precipitated with 1.5 cc. of saturated NaCl solution. The precipitate was washed twice with 2 cc. of a solution containing 0.6 volume saturated NaCl and 0.4 volume H_2O. (c) One cubic centimeter of 1:2 plasma was coagulated by the addition of 1 cc. of a 1:50,000 dilution of Crotalus adamanteus venom. The clot was thoroughly expressed on filter paper. The precipitates were digested with 1 cc. of 50 per cent H_2SO_4 and superoxol. The amino N was determined by Nesslerization. The figures

[1] Two of the three dogs which showed no retardation of coagulation were under amytal anesthesia at the time of the injection.

in the body of Table II indicate the fibrinogen N in milligrams per cc. of plasma.

EXPERIMENTAL

As shown in Table I, the injection of the shocking dose of antigen caused a definite prolongation of the coagulation time in the majority of the animals. This was most marked in the dogs. In nine of these,

TABLE I

The effect of anaphylactic shock on the coagulation time of 6 rabbits and 11 dogs

ANIMAL NUMBER		SPONTANEOUS COAGULATION TIME, IN MINUTES		COAGULATION TIME OF RECALCIFIED CITRATED PLASMA,* IN MINUTES	
		Before shock	After shock	Before shock	After shock
Rabbits	1	3	15	9½	25
	2	1½	5	13	35
	3	5	15	3	40
	4	5	>100	14	25
	5	11	>30	5	30
	6	5	7	21	38
Dogs	1	<2	180	—**	
	2	3	Non-coagulable	—	
	3	<3	Non-coagulable	—	
	4	<5	Non-coagulable	—	
	5	2	Non-coagulable	—	
	6	2	Non-coagulable	—	
	7		—**	2½	15
	8		—	3¼	Non-coagulable
	9		—	3½	45
	10	2	Non-coagulable		
	11		Non-coagulable		

* The coagulation time on the addition of the optimum quantity of 1 per cent $CaCl_2$ solution.

** Not done.

the blood withdrawn five to thirty minutes after the shocking injection remained fluid indefinitely. Even when coagulation occurred, it was often incomplete, and the clot consisted of a soft, jelly-like mass which did not adhere to the container, but was suspended in the remaining unclotted blood.

Samples of blood from each animal were also drawn into citrate (forty volumes of blood into one volume of twenty per cent citrate)

immediately before the shocking injection and five to thirty minutes later. The fibrinogen content of the citrated plasmas was determined by direct Kjeldahl analysis of: (a) the precipitate obtained by heating at 56°C.; (b) the precipitate obtained on the addition of 1.5 volumes of saturated sodium chloride, and (c) the fibrin clot formed on the addition of Crotalus adamanteus venom to the plasma. As is

TABLE II

The effect of anaphylactic shock on the fibrinogen content of dog and rabbit plasma

ANIMAL NUMBER			MG. FIBRINOGEN N PER CC. PLASMA AS DETERMINED BY		
			COAGULATION AT 56°C.	SALTING WITH NaCl	COAGULATION WITH CROTALUS ADAMANTEUS VENOM
Rabbits	8	Before shock	1.26	1.32	1.26
		After shock	1.28	1.48	1.20
	9	Before shock	—*	—	—
		After shock	0.48	0.64	—
	10	Before shock	0.46	0.56	0.52
		After shock	0.40	0.34	0.34
	11	Before shock	1.90	—	2.6
		After shock	2.14	3.34	—
Dogs	10	Before shock	1.08	1.40	—
		After shock	1.40	1.39	1.78
	11	Before shock	1.38	—	—
		After shock	0.9	—	0.94
	12	Before shock	1.06	1.18	1.24
		After shock	1.06	1.14	—

* Not done.

seen in Table II, no significant or regular difference could be demonstrated between the samples drawn before and after shock. The retardation of coagulation caused by anaphylactic shock could therefore not be due to fibrinogen deficiency.

On *a priori* grounds, one would not expect the retarded coagulation to be caused by a decreased platelet count. The amount normally

present is many times the minimum necessary for coagulation within normal time limits (8a), and only their complete disappearance would account for the absolute non-coagulability frequently noted. As is shown in Table III, although there was usually a significant decrease in the platelet count after anaphylactic shock, the amount remaining would have sufficed to effect coagulation within approximately normal time limits. Moreover, it is to be noted that there was a similar

TABLE III

The effect of anaphylactic shock on the platelet count of three dogs and five rabbits

ANIMAL NUMBER		DEGREE OF SHOCK	COAGULATION TIME IN MINUTES		PLATELET COUNT[2]	
			Before shock	After shock[1]	Before shock	After shock[1]
Dogs	10	Increased respiratory rate	2	Non-coagulable	362,000	82,000[3]
	11	Death in 10 minutes	3	Non-coagulable	286,000	213,000
	12	No definite effect	2½	Non-coagulable	418,000	200,000
Rabbits	7	Increased respiratory rate; weakness	5	45	283,000	99,000[3]
	8	Death in 3 minutes	8	35	734,000	[3]
	9	Slight	4	6	555,000	272,000
	10	Moderate	3	15	834,000	382,000
	11	Moderate	5	18	1,048,000	530,000[3]

[1] Blood withdrawn 5 to 15 minutes after the shocking injection.

[2] Of the citrated plasma obtained either by spontaneous sedimentation or by very slow centrifugation.

[3] Definite, and as yet unexplained, agglomeration of the platelets into large hyaline clumps which rendered the count of dubious significance. This clumping may be the cause of the reduction almost regularly observed in the platelet count after anaphylactic shock.

decrease in platelet count in animals in which the coagulation time was only slightly affected; conversely, there was no significant decrease in several animals which showed a markedly prolonged coagulation time. Finally, and most significant, the addition of platelet suspension or of cephalin to dog plasma rendered non-coagulable by anaphylactic shock did not effect its coagulation. The conclusion seems justified that, as in the case of fibrinogen, the retarded coagulation caused by anaphylactic shock is not primarily due to a decrease in the platelet count. Nevertheless, the decrease almost regularly observed may

well be somehow related either to the shock or to the retarded coagulation, and deserves further study, particularly in view of the clumps of platelets seen in several of the plasmas (*cf.* footnote to Table III).

TABLE IV

The susceptibility of citrated rabbit plasma to coagulation by thrombin before and after anaphylactic shock

To 0.4 cc. of citrated plasma were added 0.4 cc. of salt solution and varying amounts of citrated rabbit thrombin contained in 0.4 cc. The figures in the body of the table represent the coagulation time in minutes.

ANIMAL NUMBER		AMOUNT OF THROMBIN ADDED TO PLASMA, CC.						APPROXIMATE INCREASE IN AMOUNT OF THROMBIN NECESSARY TO PRODUCE COAGULATION*
		0.4	0.2	0.1	0.05	0.025	0.0125	
1	Before shock	2	3	4½	8	15	45	>32
	After shock	No clot in 120 minutes						
2	Before shock	2½	3	4½	9	16		>32
	After shock	No clot in 120 minutes						
3	Before shock	5	6½	10½	30			>16
	After shock	No clot in 120 minutes						
4	Before shock	1	1¾	3½	6½	15		20±
	After shock	25 (soft) 120. No coagulation						
5	Before shock	2¾	3½	7½	11	23		16±
	After shock	22 (soft). No clot in 120 minutes						
6	Before shock	7	9	13	20			10±
	After shock	28 (soft). No clot in 120 minutes						

* This was estimated as follows (3): a graph was constructed for each horizontal row of figures in the Table, correlating thrombin concentration and coagulation time. By graphic interpolation, the amount of thrombin necessary to produce coagulation in some arbitrarily fixed interval (e.g., 15, 30 or 60 minutes) was then determined. The regular increase caused by anaphylactic shock is expressed in the last vertical column of the Table as a multiple of the amount which normally sufficed.

When an attempt was made to coagulate the several plasmas by the addition of thrombin, a striking decrease was found in the coagulability of the plasma after anaphylactic shock. As seen in Tables IV and V, 10 to 200 times as much thrombin was required to effect coag-

ulation. In order to obtain a direct measure of the relative antithrombic activity of the blood before and after anaphylactic shock,

TABLE V

The susceptibility of citrated dog plasma to coagulation by thrombin before and after anaphylactic shock

To 0.4 cc. of citrated plasma were added 0.4 cc. of salt solution and varying amounts of citrated dog thrombin, contained in 0.4 cc. The figures in the body of the table represent the coagulation time in minutes.

ANIMAL NUMBER		AMOUNT OF THROMBIN ADDED TO PLASMA, CC.							APPROXIMATE INCREASE IN AMOUNT OF THROMBIN NECESSARY TO PRODUCE COAGULATION*
		0.4	0.2	0.1	0.05	0.025	0.0125	0.0062	
1	Before shock	<1	<1	<1	1	3	4	9	2–3
	After shock	<1	<1	1	1½	4	14 (soft)	30	
2	Before shock				6	14	25		1½
	After shock				7	23	>60		
3	Before shock				1	2	3	6½	60
	After shock	5½	12	Non-coagulable					
4	Before shock				1½	2½	4	10	30
	After shock	2½	6	Non-coagulable					
5	Before shock	<1	<1	<1	1	1½	3	6	>200
	After shock	Non-coagulable							
6	Before shock	<½	<½	<½	¾	1½	3	4	>200
	After shock	Non-coagulable							
7	Before shock	<½	<½	½	1½	2	4¾	18(?)	64
	After shock	70	Non-coagulable						
8	Before shock	<½		<½	1	2	4½	8	>200
	After shock	Non-coagulable							
9	Before shock	<½		¾	1¼	2¼	5	12	150±
	After shock	70	Non-coagulable						

* See footnote to Table IV.

varying amounts of clear dog plasma were added to a constant amount of purified fibrinogen solution. The mixture was brought to constant volume, and a fixed amount of thrombin then added. The

TABLE VI

The antithrombic activity of dog plasma before and after anaphylactic shock

Varying amounts of each plasma were brought up to 0.4 cc. with 0.85% NaCl, 0.4 cc. of fibrinogen were added to each tube, and 0.4 cc. of a thrombin dilution. The figures in the body of the table represent the coagulation time in minutes.

ANIMAL NUMBER		AMOUNT OF CLEAR PLASMA ADDED TO FIBRINOGEN PRIOR TO ADDITION OF FIXED AMOUNT OF THROMBIN, CC.*							APPROXIMATE INCREASE IN THE ANTITHROMBIC ACTIVITY OF PLASMA AFTER ANAPHYLACTIC SHOCK**
		0.4	0.2	0.1	0.05	0.025	0.125	0.0062	
1	Before shock	3		1½		1	¾		4±
	After shock	8	5	4	1¾	1½	1¼	1	
2	Before shock	3½	3	2½	1¾	1	¾		8±
	After shock	12	12	8½	4½	1	¾		
3	Before shock	3	2½	2	1½	1	¾	¾	40
	After shock	Non-coagulable					12	1¼	
4	Before shock	4½	3½	1¾		1½	1		10
	After shock	Non-coagulable			12	4	1	1	
5	Before shock	3	2½	2	1½	1	¾		60
	After shock	Non-coagulable					60	2½	
6	Before shock	2½	2	1½	1½	1	¾		60
	After shock	Non-coagulable					60	2½	
7	Before shock	12	8	6½	6½	4½	3¾	3¾	10
	After shock	Non-coagulable				7	4¼	4	
8	Before shock	6	5¾	4¾	4½		4	3½	100
	After shock	Non-coagulable						8	
9	Before shock	7	6½	6	5	4½	3¾	3½	50
	After shock	Non-coagulable					9	<5	

* In experiments 1 to 6, dog thrombin was used in a 1:16 dilution. In experiments 7 to 9, a different thrombin preparation was used in a 1:32 dilution.

** This was estimated as follows: a graph was constructed for each horizontal row of figures in the Table, correlating the amount of plasma used with the observed coagulation time. For each animal some arbitrary time was selected (*e.g.*, 10, 20, or 60 minutes), and the amount of heated plasma necessary to prolong coagulation to this level was determined by graphic interpolation. Anaphylactic shock regularly and markedly decreased the amount of plasma necessary to effect this retardation. This is expressed in the last vertical row as a multiple of the normal antithrombic activity of the plasma. Thus, if 0.4 cc. of plasma were normally required to prolong the coagulation time to 12 minutes, and if 0.028 cc. sufficed after anaphylactic shock, the increase in antithrombic activity was 0.4/0.028, or 14-fold.

results are summarized in Table VI. Anaphylactic shock caused as much as a hundred-fold increase in the antithrombic activity of the plasma.

In the plasmas exhibiting the greatest antithrombic activity, prothrombin could not be demonstrated either by the addition of tissue extract and calcium to the citrated plasma, or by the precipitation of the diluted plasma with acetic acid, which normally precipitates a large proportion of the plasma prothrombin along with some of the fibrinogen (6). It is, however, probable that prothrombin was present in these plasmas, and was merely masked by the excessive amount of antithrombin. In the first place, the apparently prothrombin-free acetic acid precipitates were definitely antithrombic, and sufficiently so to neutralize any thrombin which may have been formed. In the second place, prothrombin could be regularly demonstrated in those plasmas in which the antithrombin activity was only increased e.g. 5- to 20-fold. In such plasmas, the addition of calcium and tissue extract (or platelets) regularly caused coagulation, probably because the elaboration of thrombin was sufficiently rapid to overcome the inhibitory antithrombin and coagulate the fibrinogen.[2] The acetic-acid precipitate from such plasmas also contained demonstrable prothrombin in approximately normal concentration. Finally, and perhaps most significant, the antithrombic activity of these plasmas was regularly reduced to a small fraction of its original level by the addition of calcium; and in some cases the antithrombic activity completely disappeared (*cf.* Table VII). The result is difficult to explain on any basis other than the presence in these plasmas, even those apparently non-coagulable, of significant amounts of prothrombin. On the activation of this prothrombin by the addition of calcium, the formed thrombin would combine with a large proportion of antithrombin, and the decreased antithrombic activity of the calcified mixture would reflect this combination. Presumably for the same reason, blood drawn into citrate was always far more antithrombic

[2] Contrary to the opinions of Lee and Vincent, or Schultz, such coagulation does not necessarily imply that platelets are the missing factor in blood after anaphylactic shock (*cf.* Pepper and Krumbhaar). Platelets would accelerate thrombin production and coagulation regardless of the factor responsible for the retardation (*cf.* Eagle, 1935).

than blood collected without an anticoagulant. These several observations indicate the presence of prothrombin even in the non-coagulating blood samples. The observed retardation of coagulation cannot be primarily due to a prothrombin deficiency.[3]

The present experiments offer no indication as to whether the antithrombic substance demonstrated in the blood after anaphylactic

TABLE VII

The effect of calcium on the antithrombic activity of anaphylaxis plasma

To the dog plasmas listed as 1 to 5 in Table VI were added ½ volume of 1 per cent $CaCl_2$ and their antithrombic activity re-tested after 30 minutes at room temperature by the same method as that used for the experiment of Table VI. The figures in the body of the table represent coagulation time in minutes.

ANIMAL NUMBER		AMOUNT OF PLASMA ADDED TO FIBRINOGEN PRIOR TO ADDITION OF FIXED AMOUNT OF THROMBIN						APPROXIMATE REDUCTION IN ANTITHROMBIC ACTIVITY EFFECTED BY ADDITION OF $CaCl_2$*
		0.4	0.2	0.1	0.05	0.025	0.0125	
								per cent
1	Before Ca	8	5	4	1¾			50
	After Ca	5	4	2	1			
2	Before Ca	12	12	8½	4½	2	1½	100
	After Ca	No antithrombin: fluid *thrombic*						
3	Before Ca	No coagulation					12	80–90
	After Ca	Shreds		20	9	4	2	
4	Before Ca	No coagulation		12	4	1		80–90
	After Ca	3½	2		1½			
5	Before Ca	Non-coagulable					60	>80
	After Ca	60 (soft)			40			

* Cf. Footnote to Table VI for method used in evaluating antithrombic activity.

shock also prevents the transformation of prothrombin to thrombin. The chemical properties of the antithrombin, its mode of action, and its relationship to that normally present in blood, as well as that elaborated after peptone shock, are subjects for further study.

[3] Several experiments to estimate the prothrombin content of the non-coagulating plasmas on the basis of their decreased antithrombic activity after the addition of calcium failed to give any clear-cut results, first, because of the slowness of the reaction between thrombin and antithrombin, and second, because they apparently do not combine in a fixed ratio.

SUMMARY

The retarded coagulation observed in six rabbits and eleven dogs immediately after anaphylactic shock was regularly associated with the presence of increased amounts of antithrombin in the blood. The increased antithrombic activity was as much as one hundred times the normal level.

The fibrinogen content of the plasma was not significantly affected; for the reasons cited in the text, there is reason to believe that even the plasmas completely non-coagulable by calcium and tissue extract nevertheless contained sufficient prothrombin to effect coagulation; and although the platelet count was usually decreased after anaphylactic shock, the amount remaining would ordinarily have sufficed to cause coagulation within approximately normal time limits.

The increased antithrombic activity of the blood after anaphylactic shock is apparently the primary cause of the observed retardation of coagulation.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Essentials of Electrocardiography. By RICHARD ASHMAN, Ph.D., and EDGAR HULL, M.D. 212 pp. Ill. $3.50. (*The Macmillan Company, New York, 1937.*)

A new work in the field of electrocardiography, the present volume is designed particularly to aid the student and practitioner of medicine to a better understanding of the uses and limitations of the electrocardiogram.

The presentation is clear and concise. The reviewer, however, wishes to register disapproval of the use of the word *pathology* where *disease* is intended. An excellent bibliography at the end of each chapter compensates for what at times appears to be rather brief treatment of a subject. Of particular interest to any one concerned with electrocardiographic interpretation is the table of normal values included in the appendix.

The book is excellently printed on a good grade of paper, and is of a convenient size. It may be read with profit by any one interested in clinical electrocardiography.

R. F.

Greek Medicine. By FRED B. LUND. 161 pp. 7 illus. $2.00. (Clio Medica, xviii.) (*Paul B. Hoeber, Inc., New York, 1936.*)

In relatively small space, Dr. Lund has succeeded in giving an outline of the development of Greek medicine from its legendary beginnings down to its late outposts in medieval Byzantium. Presenting more than the title promises, he has also included a sketch of Roman medicine and discusses such Latin authors as Celsus, Pliny and Caelius Aurelianus. The book is well arranged and the parts dealing with surgery are comparatively the best. It is to this subject that many of the incorporated translations of Greek texts refer.

Since our factual knowledge of ancient medicine is fragmentary, our picture largely depends on the personal views and interpretations of the historian. This makes it all the more necessary for him to have his data correct and in congruence with latest research. Unfortunately this is very often not the case in the present book. Thus, *e.g.*, Galen was certainly not the "originator" (p. 105) of the macrocosm-microcosm analogy; yellow bile was considered hot and dry and not "cold and moist" (p. 27), and Gargilius Martialis wrote on "medicinae ex *oleribus* et pomis" and not from some unfortunate *clericis* (p. 138). On page 105 the author translates "spirits (pneumata)" where the Galenic text (ed. Kühn X, 635) has

"psychas," *i.e.*, souls. And since Herzog and Schazmann showed in 1932 that the cult of Asclepius in Cos only dates back to the middle of the 4th century B.C., the old story which made Hippocrates a priest of Asclepius (p. 12) ought not to be repeated.

Such mistakes have a fatal tendency to be inherited and are regrettable in a book which will probably find many readers amongst students and physicians.

O. T.

Contraception as a Therapeutic Measure. By BESSIE L. MOSES. 106 pp. $1.00. (*Williams & Wilkins Company, Baltimore, 1936.*)

This book, rather than being a plea for, or an explanation of, modern contraception, is a statistical study of a group of over a thousand women who were treated at the Bureau for Contraceptive Advice in Baltimore over a period of five years.

All the patients were referred to the Bureau by physicians because of some medical indication. They came from a large number of practitioners.

Most of the patients were interviewed and treated, or the treatment supervised, by the author, which in itself eliminates one confusing element in a statistical study of this kind.

The data analyzed from the records include the various indications for referring the patients to the Bureau; the number of abortions in the group, and the previous use and efficacy of contraceptives.

There is a separate section analyzing the follow up work, the incidence of pregnancies in the group with an attempt to explain the failures of the method.

A discussion of the methods advised and the materials used is included in one chapter but the author makes no attempt to go into the details of the methods of instruction.

Dr. Moses accomplishes her purpose in the book briefly and clearly and it can be regarded as a valuable contribution to the literature on the subject.

J. H. L.

The Endocrine Organs in Health and Disease with an Historical Review. By SIR HUMPHRY DAVY ROLLESTON, Bart. 521 pp. Illus. $13.00. (*Oxford University Press, London, 1936.*)

In his preface the author states that this volume is the result of the delivery of four lectures on the History of the Endocrine Organs at the Royal College of Physicians of London. In the reviewer's opinion, the work is a classic on the historical background and evolution of modern endocrinology. Far more space is devoted to the history of the glandular disorders than to the clinical descriptions of hormonological abnormalities. The volume will therefore always have great value in any library, whereas works especially emphasizing other aspects of so young and rapidly advancing a branch of medicine will necessarily soon become obsolete. The subject matter is discussed with a conservative insight into the many problematical points possible only to one of the author's wide experience in

pathology and clinical medicine. The publishers have set a high price on it ($13.00), but the bibliography alone is worth the price. This reviewer recommends it highly to students of endocrinology, and no medical library can afford to be without it.

J. E. H.

Into This Universe. The Story of Human Birth. By ALAN FRANK GUTTMACHER. 366 pp. Illus. $2.75. (*The Viking Press, New York, 1937.*)

This volume of 365 pages forms a companion piece to "Life in the Making" by the same author, the latter dealing with human procreation and the former with human birth. Dr. Guttmacher is to be commended for presenting a difficult and frequently controversial material in a manner which cannot offend the physician and should interest and instruct the layman. One feels a deliberate attempt, and a successful one, to avoid the spectacular; and without sacrificing interest a dignified tone is maintained. The sections on obstetric abnormalities, while adequate, are not overemphasized and should not be alarming to the lay reader. Of particular merit is Chapter 2, dealing with pregnancy and labor according to sixteenth century customs and standards. In the reviewer's opinion here, at last, is a text which can be given with benefit to the expectant mother and without fear of psychic trauma.

C. H. P.

The Management of Obstetric Difficulties. By PAUL TITUS. 879 pp. Illus. $8.50. (*C. V. Mosby Company, St. Louis, 1937.*)

As the title of this volume suggests, it is intended as "a practical aid to physicians who are meeting and contending with obstetric difficulties and emergencies." Since this is so, the author has omitted from its contents many of the fundamentals of the obstetric art, including the management of normal pregnancy, labor, and the puerperium. In the opinion of the reviewer this is a misfortune, for a more thorough knowledge of fundamentals is frequently the practicing physician's greatest need. Abnormal obstetrics is dealt with comprehensively and generally in a conservative and sane manner. Certain of the author's recommendations on debatable topics seem rather dogmatic but, as he states, he has not hesitated to express his own views on undecided issues. The illustrations, although not profuse, are commendable. The bibliography needs bringing up to date: for example, that relating to puerperal infection contains no reference to the important work of Colebrook and his associates. The most praiseworthy section is that referring to sterility which is discussed in a practical and intelligent manner. As a reference work in a time of emergency the book merits a place on the library shelf.

C. H. P.

The Lung. By WILLIAM SNOW MILLER. 209 pp. Illus. $7.50. (*Charles C. Thomas, Springfield, Illinois, 1937.*)

This anatomical study of the lung reflects largely the contributions of the

author who has for so long devoted himself to the many problems which have roused discussion. The architecture of the bronchi and bronchioles has not caused such difficulties as have been met with in the more distal portions of the alveoli where many doubt the existence of an epithelial lining. But the author rightly appeals to pathological conditions which readily demonstrate such a lining in its continuity with that of the atria and ductuli. The relations of the pulmonary and bronchial arteries are clearly brought out and there is long discussion of the course of lymphatics based on the arrangement of the valves. This would lead to the belief that one set—namely, the deep pulmonary lymphatics—is distinct from a superficial set which empties into the pleural network which also finally empties into the tracheo-bronchial lymph nodes. Nothing is said of the relation of these lymphatics to the pleural cavity.

The book ends with a historical sketch in which the work of each contributor is summarized.

W. G. M.

Diseases of the Newborn. By ABRAHAM TOW. 477 pp. Illus. (*Oxford Medical Publications. Oxford University Press, New York, 1937.*)

Doctor Tow has completed a splendid job in giving us a much needed text and reference book on the newborn infant. His bibliography is exhaustive, well organized and constitutes the outstanding feature of this book. The table of contents is unusually complete and the book is well indexed except for the omission of an Authors' Index which is always an aid to one who uses a textbook for reference purposes. The illustrations are neither so well chosen nor numerous enough to satisfy the average physician.

The material itself is presented in a typical concentrated American manner, which makes for relatively uninteresting reading. The American physician, about to write a textbook, would do well to study the pleasing style of the Englishman in the presentation of his material. Nevertheless, the author has written a fine reference volume which is a real contribution to the obstetric and pediatric literature.

A. C.

Roentgen Interpretation. By GEORGE W. HOLMES and HOWARD E. RUGGLES. 5th ed. 356 pp. Illus. $5.00. (*Lea & Febiger, Philadelphia, 1936.*)

Holmes and Ruggles' "Roentgen Interpretation" now appears in its 5th edition and the authors are to be congratulated upon their earnest desire to keep this work up to date. It is regrettable that so many excellent works go by the board simply because the authors will not persevere in keeping them up to date.

As a beginner's textbook on roentgenological interpretation it has no peer and it should adorn the library of every roentgenologist. The one criticism that seems justifiable is its brevity, but at the end of each chapter one finds appended a moderately complete bibliography.

On the whole the book is a ready reference work and is filled with the fundamentals of x-ray interpretation. Even the experienced radiologist should feel more secure with such a book at hand.

C. A. W.

BOOKS RECEIVED

Post-Mortem Appearances. By JOAN M. ROSS. 3rd ed. 243 pp. $2.50. Oxford University Press, New York and London, 1937. (Oxford Medical Publications)

Medical Greek and Latin at a Glance. By WALTER R. AGARD. 87 pp. $1.50. Paul B. Hoeber, Inc., New York, 1937.

Clinical Laboratory Diagnosis. By SAMUEL A. LEVINSON and ROBERT P. MACFATE. 877 pp. Illus. $9.50. Lea & Febiger, Philadelphia, 1937.

The Intimate Side of a Woman's Life. By LEONA W. CHALMERS. Pioneer Publications, Inc., New York, 1937.

Surgical Pathology of the Thyroid Gland. By ARTHUR E. HERTZLER. 298 pp. Illus. $5.00. J. B. Lippincott Co., Philadelphia, 1936. (Hertzler's Monographs on Surgical Pathology)

Traité de Biocolloïdologie. By W KOPACZEWSKI. Tome IV, Etat colloïdal et biologie. Fasc. VI, Narcose. 164 pp. 35 fr. Unbound. Gauthier-Villars, Paris, 1936.

Handbook of Orthopaedic Surgery. By ALFRED RIVERS SHANDS. 593 pp. Illus. $5.00. C. V. Mosby Company, St. Louis, 1937.

Estudos Cirurgicos. By EURICO BRANCO RIBEIRO. 2.ª serie. 245 pp. Illus. Sociedade Editora Medica Limitada, São Paulo, Brasil, 1936.

National Health Series. Funk and Wagnalls Company, New York, 1937. 35 cents each or three for $1.00.

Taking Care of your Heart. By T. STUART HART. 110 pp.

Venereal Diseases. By WILLIAM FREEMAN SNOW. 98 pp.

How to Sleep and Rest Better. By DONALD A. LAIRD. 83 pp. Illus.

Exercise and Health. By JESSE FEIRING WILLIAMS. 70 pp. Illus.

The Common Cold. By WILSON G. SMILLIE. 77 pp. Illus.

The Common Health. By JAMES A. TOBEY. 96 pp.

The Healthy Child. By HENRY L. K. SHAW. 108 pp.

The Expectant Mother and her Baby. By ROBERT L. DENORMANDIE.

Adolescence. By MAURICE A. BIGELOW. 99 pp.

What You Should Know about Eyes. By F. PARK LEWIS. 82 pp.

The Management of Obstetric Difficulties. By PAUL TITUS. 879 pp. Illus. $8.50. C. V. Mosby Co., St. Louis, 1937.

Heart Disease. By PAUL DUDLEY WHITE. 2nd ed. 744 pp. Illus. $7.50. The Macmillan Company, New York, 1937.

An Introduction to Pharmacology and Therapeutics. By J. A. GUNN. 5th ed. 240 pp. 5 sh. Humphrey Milford, Oxford University Press, 1936.

INDEX TO VOLUME LX

Adenitis, mesenteric, A puzzling case of obstipation apparently due to..... 40
Albright, Fuller, Truman G. Drake and Hirsh W. Sulkowitch: Renal osteitis fibrosa cystica: Report of a case with discussion of metabolic aspects..... 377
Anaphylactic shock, On the prolonged coagulation time subsequent to..... 428

Bard, Philip, and David McK. Rioch: A study of 4 cats deprived of neocortex and additional portions of the forebrain..... 73
Bliss, Eleanor A., and Perrin H. Long: The activation of "prontosil solution" *in vitro* by reduction with cysteine hydrochloride..... 149
Book Reviews.....56, 154, 215, 307, 374, 439
Breast, carcinoma of the, The use of a muscle pedicle flap for prevention of swelling of the arm following the radical operation for, Preliminary report..... 369
Bronchus, main, A new operative technique for closure of the, Preliminary report... 372

Clason, Freeman P., Francis F. Schwentker, William A. Morgan, Janvier W. Lindsay and Perrin H. Long: The use of para-amino-benzine-sulphonamide or its derivatives in the treatment of beta haemolytic streptococcal meningitis..... 297

Drake, Truman G., Fuller Albright and Hirsh Sulkowitch: Renal osteitis fibrosa cystica: Report of a case with discussion of metabolic aspects..... 377

Eagle, Harry, C. G. Johnston and I. S. Ravdin: On the prolonged caogulation time subsequent to anaphylactic shock..... 428
Emerson, Kendall, Jr.: On the specificity of the thyreotropic action of the anterior pituitary gland..... 358

Felton, Lloyd D., and Frank B. Wakeman: Essential immunizing antigen of the typhoid bacillus..... 178
Ford, Frank R., and Harriet Guild: Precocious puberty following measles encephalomyelitis and epidemic encephalitis, with a discussion of the relation of intracranial tumors and inflammatory processes to the syndrome of macrogenitosomia praecox..... 192
Furstenberg, Frank F., and Leslie N. Gay: The occurrence of constitutional reactions in the treatment of hay-fever and asthma: Analysis of the causative factors... 412

Gantt, W. Horsley, S. Katzenelbogen and R. B. Loucks: An attempt to condition hyperglycemia to adrenalin..... 400
Gay, Leslie N., and Frank F. Furstenberg: The occurrence of constitutional reactions in the treatment of hay-fever and asthma: Analysis of the causative factors... 412
Guild, Harriet, and Frank R. Ford: Precocious puberty following measles encephalomyelitis and epidemic encephalitis, with a discussion of the relation of intracranial tumors and inflammatory processes to the syndrome of macrogenitosomia praecox..... 192

Hay-fever and asthma, The occurrence of constitutional reactions in the treatment of, Analysis of the causative factors..... 412
Hesser, Frederick H., and Orthello R. Langworthy: Reflex vesical contraction in the cat after transection of the spinal cord in the lower lumbar region..... 204
Hines, Marion: The "motor" cortex..... 313
Hyperglycemia to adrenalin, An attempt to condition..... 400

Johnston, C. G., Harry Eagle and I. S. Ravdin: On the prolonged coagulation time subsequent to anaphylactic shock..... 428

Katzenelbogen, S., W. Horsley Gantt and R. B. Loucks: An attempt to condition hyperglycemia to adrenalin..... 400
Kellaway, Charles H.: Snake venoms. I. Their constitution and therapeutic applications. II. Their peripheral action. III. Immunity..... 1, 18, 159
Kemp, Jarold E., and Paul D. Rosahn: Experimental study of congenital syphilis, including a study of the infectiousness of blood, uterus and placenta of pregnant rabbits with early syphilis..... 45

Langworthy, Orthello R., and Frederick H. Hesser: Reflex vesical contraction in the cat after transection of the spinal cord in the lower lumbar region..... 204
Langworthy, Orthello R.: A curious illustration of "mass reflex" and involuntary micturition following injury of the spinal cord..... 337
Lindsay, Janvier W., Francis F. Schwentker, Freeman P. Clason, William A. Morgan and Perrin H. Long: The use of para-amino-benzine-sulphonamide or its derivatives in the treatment of beta haemolytic streptococcal meningitis..... 297
Long, Perrin H., and Eleanor A. Bliss: The activation of "prontosil solution" *in vitro* by reduction with cysteine hydrochloride..... 149
Long, Perrin H., Francis F. Schwentker, Freeman P. Clason, William A. Morgan, Janvier W. Lindsay: The use of para-amino-benzine-sulphonamide or its derivatives in the treatment of beta haemolytic streptococcal meningitis..... 297
Longcope, Warfield T., and J. William Pierson: Boeck's sarcoid (sarcoidosis)..... 223
Loucks, R. B., W. Horsley Gantt and S. Katzenelbogen: An attempt to condition hyperglycemia to adrenalin..... 400

Macrogenitosomia praecox, Precocious puberty following measles encephalomyelitis and epidemic encephalitis, with a discussion of the relation of intracranial tumors and inflammatory processes to the syndrome of..... 192
Mass reflex and involuntary micturition following injury of the spinal cord, A curious illustration of..... 337
Meningitis, streptococcal, The use of para-amino-benzine-sulphonamide or its derivatimes in the treatment of beta haemolytic..... 297
Morgan, William A., Francis F. Schwentker, Freeman P. Clason, Janvier W. Lindsay and Perrin H. Long: The use of para-amino-benzine-sulphonamide or its derivatives in the treatment of beta haemolytic streptococcal meningitis..... 297
Motor cortex, The..... 313

Neocortex and additional portions of the forebrain, A study of four cats deprived of..... 73

Nicholson, William M., and Abraham J. Schechter: Cardiac arrhythmia after bilateral ureteral ligation in the dog..... 346

Osteitis fibrosa cystica, Renal: Report of a case with discussion of metabolic aspects..... 377

Pierson, J. William, and Warfield T. Longcope: Boeck's sarcoid (sarcoidosis)..... 223
"Prontosil solution," Activation of, *in vitro* by reduction with cysteine hydrochloride. 149

Ravdin, I. S., Harry Eagle and C. G. Johnston: On the prolonged coagulation time subsequent to anaphylactic shock..... 428
Rienhoff, William Francis, Jr.: The use of a muscle pedicle flap for prevention of swelling of the arm following the radical operation for carcinoma of the breast. Preliminary report..... 369
Rienhoff, William F., Jr.: A new operative technique for closure of the main bronchus. Preliminary report..... 372
Rioch, David McK., and Philip Bard: A study of four cats deprived of neocortex and additional portions of the forebrain..... 73
Rosahn, Paul D., and Jarold E. Kemp: Experimental study of congenital syphilis, including a study of the infectiousness of blood, uterus and placenta, of pregnant rabbits with early syphilis..... 45

Sarcoid (sarcoidosis), Boeck's..... 223
Schechter, Abraham, and William M. Nicholson: Cardiac arrhythmia after bilateral ureteral ligation in the dog..... 346
Schwentker, Francis F., Freeman P. Clason, William A. Morgan, Janvier W. Lindsay and Perrin H. Long: The use of para-amino-benzine-sulphonamide or its derivatives in the treatment of beta haemolytic streptococcal meningitis..... 297
Snake venoms. I. Their constitution and therapeutic applications. II. Their peripheral action. III. Immunity..... 1, 18, 159
Sulkowitch, Hirsh W., Fuller Albright and Truman G. Drake: Renal osteitis fibrosa cystica: Report of a case with discussion of metabolic aspects..... 377
Syphilis, congenital, Experimental study of, including a study of the infectiousness of blood, uterus and placenta, of pregnant rabbits with early syphilis..... 45

Thyreotropic action of the anterior pituitary gland, On the specificity of the..... 358
Trimble, I. Ridgeway: A puzzling case of obstipation apparently due to mesenteric adenitis..... 40
Typhoid bacillus, Essential immunizing antigen of the..... 178

Ureteral ligation, bilateral, in the dog, Cardiac arrhythmia after..... 346

Vesical contraction, Reflex, in the cat after transection of the spinal cord in the lower lumbar region..... 204

Wakeman, Frank B., and Lloyd D. Felton: Essential immunizing antigen of the typhoid bacillus..... 178

John Whitridge Williams: Academic Aspects and Bibliography. By J. Morris Slemons. Foreword by John C. French. 1935. 121 pages, frontispiece, 12mo, boards, $1.50.

The life of John Whitridge Williams, as Dr. Slemons has told the story, is an essential chapter in the history of American medicine. Dr. Williams shared largely in the far-reaching effect The Johns Hopkins School of Medicine has had on instruction and research and as a brilliant investigator in his own specialty and the author of an authoritative textbook, he advanced scientific knowledge and human welfare. Dr. Slemons had been aware of the human interest of his subject; and by virtue first of intimate association as student and junior colleague and later as scientist and practitioner in the same field thousands of miles away, he has been able to bring to it both warm personal feeling and scholarly detachment. He has performed a congenial task with distinct success.

Papers and Addresses. By William Henry Welch. 1921. Three volumes, 2013 pages, 4to, $20.00.

Dr. Welch's writings are scattered through a great variety of publications, many of which are more or less inaccessible. It was accordingly decided to publish his numerous papers and addresses. These have been collated under the following headings: Volume I. Pathology, Preventive Medicine. Volume II. Bacteriology. Volume III. Medical Education, History, Miscellaneous, Bibliography, Index.

Surgical Papers of William Stewart Halsted. 1928. Two volumes, 1232 pages, illustrated, 4to, $15.00.

When one considers the number, originality and importance of Dr. Halsted's contributions to surgery and their scattered and often not readily accessible form in various journals and reports, it will be realized that the publication of his collected papers not only constitutes a worthy tribute to his memory, but also renders a welcome and much needed service in making available these significant contributions.

William Stewart Halsted: Surgeon. By W. G. MacCallum. 260 pages, 18 illustrations, 8vo, $2.75.

A brief history of the life of the first surgeon of The Johns Hopkins Hospital. Dr. Halsted, who died in 1922, was one of the four men whose names are best known in the establishment of the fame of The Johns Hopkins Medical School and Hospital. He formed a new school of surgery and trained in his own methods and modes of thought many of the men who are now prominent surgeons in this country.

Franklin Paine Mall: The Story of a Mind. By Florence Rena Sabin. 355 pages, 8 illustrations, 8vo, $2.75.

This book seeks to give the story of the development of Mall's mind and its influence on medical science and on medical education. The writer worked for twenty years under Mall and the theory of education outlined in this volume was thus learned directly from him. It is hoped that the new generation of medical students who have never known Mall may gain, through these pages, some idea of how this man has influenced their lives and that, too, they may gain an insight into the difficulties through which the generation that preceded theirs won the privileges they now enjoy. Mall is but little known to the public, but one has only to mention his name to any of his colleagues to sense that he was one of the leaders of his generation.